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UNCONVENTIONAL NUCLEOTIDE ANALOGUES—XVIII[1]

RING EXPANSION OF URIDINE HALOCARBENE ADDUCTS. SYNTHESIS OF DIAZEPINE NUCLEOSIDES

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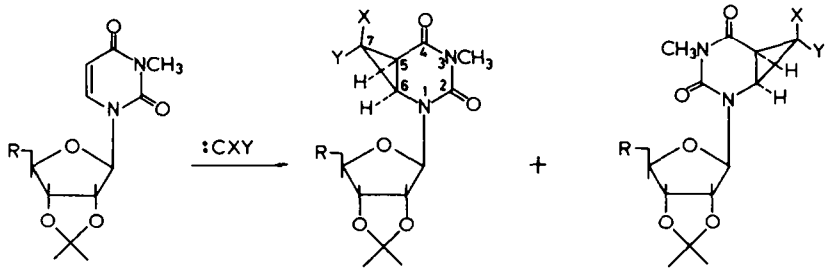
Abstract—The diastereomeric adducts of dichlorocarbene and dibromocarbene with (protected) uridine react with alcohols to give diazepine nucleosides (**4a–c**). The *endo*-chloro-*exo*-fluorocarbene adducts (**1d** and **2d**) also react analogously to yield diazepine nucleoside **4d**. On the other hand, the corresponding *exo*-chloro-*endo*-fluoro isomers (**1e** and **2e**) are totally inert under the same reaction conditions. The adducts **1b** and **2b** yield, besides the ring-expanded product (**4b**), uridine-5-aldehyde (**6a**) in varying amounts which depend upon the conformation of the diastereomer. These results are explained on the basis of a possible role of the ring-oxygen of the ribose moiety.

In the preceding paper[1] we have described the transformation of *endo*-7-chloro- or *endo* - 7 - bromo - 1,3 - diaza - 2,4 - dioxobicyclo[4,1,0]heptane derivatives—obtained by addition of halocarbenes to uracils—to the corresponding 2,4-dioxo-1,3-diazepines. We now present the application of this reaction to the convenient synthesis of diazepine nucleosides.

Addition of dihalocarbenes to suitably protected uridine resulted in the formation of mixtures of diastereomeric adducts—5R,6R (**1a-e**) and 5S,6S (**2a-e**) (Scheme 1). The structure and configurational assignments of these products have been described earlier.[3] It is pertinent for the present discussion to recall that the 5R,6R and the 5S,6S series of diastereomers exhibited the *anti*- and *syn*-conformation about the nucleoside ($C_{1'}$–N_1) bonds, respectively.

Heating of the adducts **1a–d** and **2a–d** in alcohols (t-BuOH or MeOH) gave, in each case, besides side-products—to be discussed in the sequel—the expected diazepine nucleosides **4a–d** (Scheme 2). The structure of the products was deduced from a comparison of their spectral data (Experimental) with the corresponding data of similar diazepines, obtained earlier.[1] Based upon the chemical shift of $H_{1'}$, IN **4b–d**, which lie in the range δ 5.46–5.59, *syn*-configuration may be assigned to these compounds. This would be actually the expected stereochemistry in view of the bulky nature of the t-butoxy substituent. The stereochemistry of **4a**, which consisted of a mixture of two C_7-epimers shall be discussed in the sequel. As expected the reactions of both series of diastereomers resulted in the same diazepine system. Furthermore, in accordance with the results of the thermal cyclopropane ring-opening of uracil-halocarbene adducts the *endo*-fluoro adducts **1e** and **2e** were inert under the employed reaction conditions.[1] This steric control[4a–e] of the ring-expansion process is mechanistically informative and implies a synchronous C_5–C_6 bond-cleavage and the halide expulsion step, in accord with the Woodward–Hoffmann–De Puy rule.[5a,b] The nucleophilic quenching of the carbenium ion intermediate (**3**) with alcohols can, in principle, lead to two diastereomeric diazepine nucleosides. Reaction with t-BuOH gave, however, only a single product, whose absolute stereochemistry is, as yet, undefined. On the other hand, when **1a** was heated in benzene, in presence of small amounts of methanol, two products corresponding to **4a** were formed (1:1), which could be isolated by TLC. Spectral data of the latter compounds point to their being C_7-epimers. The spectra show further that the epimers possess different conformations about the nucleoside



protected uridine
R = OAc, H

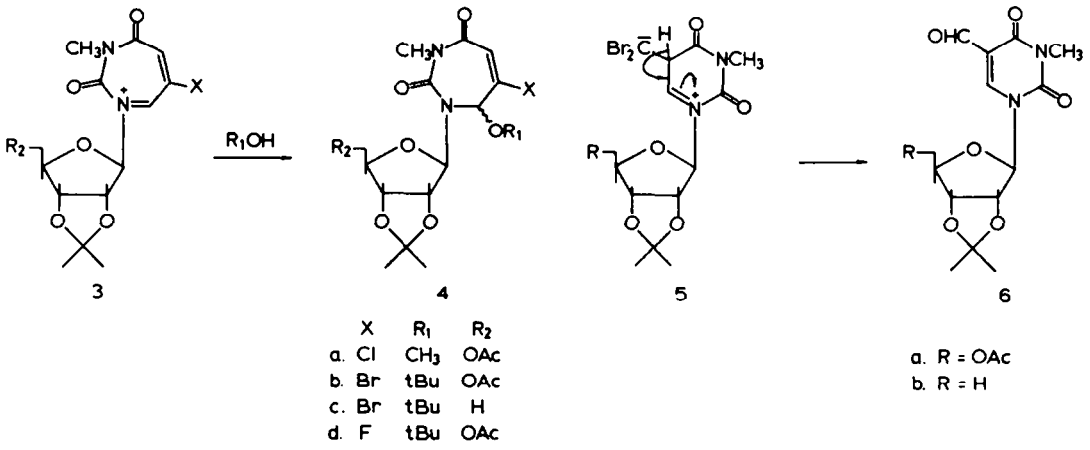
1 (anti-)

	X	Y	R
a.	Cl	Cl	OAc
b.	Br	Br	OAc
c.	Br	Br	H
d.	Cl	F	OAc
e.	F	Cl	OAc

2 (syn-)

	X	Y	R
a.	Cl	Cl	OAc
b.	Br	Br	OAc
c.	Br	Br	H
d.	Cl	F	OAc
e.	F	Cl	OAc

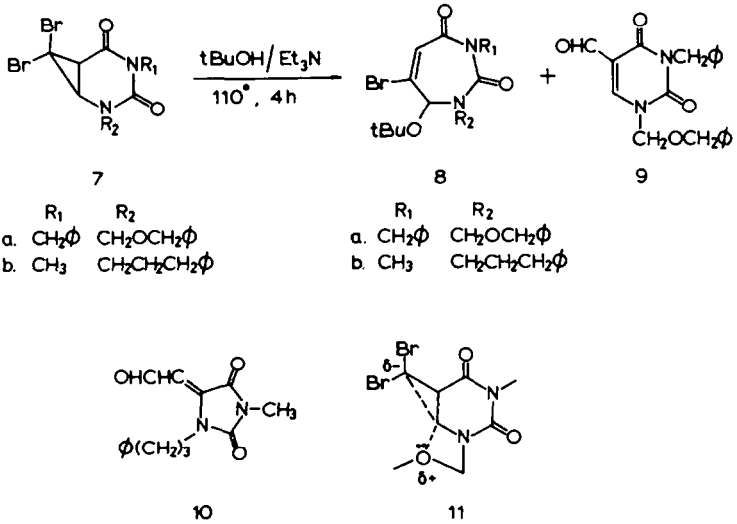
Scheme 1.



Scheme 2.

bond. Thus the $H_{1'}$ in one epimer resonates at δ 5.46 (*syn*-), while in the other it is observed at 5.83 (*anti*-). The difference in behaviour between the reactions with the two alcohols may be rationalized in terms of the steric requirements of their nucleophilic attack on intermediate **3** (X = Cl, R_2 = OAc). Presumably, the bulky t-BuOH can approach only from one side of the plane of the diazepine ring (in **3**), while the relatively small methanol can add from both sides.

As indicated earlier, the reaction of the adducts, in particular that of **1a,b** and **2a,b** does not lead exclusively to the ring expanded products. Thus, heating of **1a,b** and **2a,b** yielded, the aldehyde **6a**, in addition to the diazepine nucleosides **4a,b**.[6] Formation of **6a** can be explained by a C_6–C_7 cleavage leading to intermediate **5** (R = OAc) which, following proton loss and hydrolysis would give the aldehyde.[7] An interesting observation was the fact that the *anti*- and *syn*-diastereomers, **1b** and **2b** led to mixtures of the diazepine (**4b**) and the aldehyde (**6a**), in significantly different ratios; viz **4b**/**6a** (isolated) from **1b** and **2b** is found to be 1:3 and 3:1, respectively. A possible role of the $C_{5'}$-acetate in enhancing the C_6–C_7 cleavage (in the *anti*- diastereomer **1a**) was excluded by carrying out analogous reactions with the dibromocarbene adducts **1c** and **2c**, in which the acetate group is absent. The ratios of **4c** to **6b** formed (**1c**→**4c**/**6b** = 13%: 19%; **2c**→**4c**/**6b** = 30%: 7%) indicated that the *anti*-conformer again gave a mixture in which the aldehyde was in significant preponderance. Further attention to the question was directed by considering the potential influence, if any, of the ring-oxygen in the ribose system. To this end the model dibromocarbene adducts **7a** and **7b** (Scheme 3) were subjected to reaction with t-BuOH under identical conditions. That the O atom, in a position similar to that in the nucleoside, did indeed affect the course of the reaction, was seen in the fact that whereas **7a** yielded a mixture of **8a** and **9**; adduct **7b**, on the other hand, gave **8b** and a small amount of **10**. Aldehyde **9** was not observed in the mixture. These results suggest that the (ether) oxygen electrons may participate in the C_6–C_7 cleavage in the model **7a** and by analogy, in the similar reaction in the case of the nucleoside-carbene adducts. Although the transition-state for a lone-pair participation would involve a sterically unfavoured 4-membered ring (**11**), such an interaction would be distinctly enhanced in the carbene-adducts possessing the *anti*-conformation. The operation of this interaction is offered as an explanation for the difference in the reactivity patterns of



Scheme 3.

the diastereomers (**1b,c** + **2b,c**). The origin of hydantoin derivative **10** follows a mechanism that has been suggested earlier[1] for the formation of an analogous system from the uracil–dibromocarbene adduct.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a Unicam SP 200 spectrometer and NMR spectra were run on Varian Associates Model A-60D, HA-1000 and XL-100 instruments, using TMS as an internal standard. UV spectra were recorded on a Cary-14 spectrophotometer. Unless stated otherwise, IR and NMR spectra were taken in $CHCl_3$ and $CDCl_3$, respectively. The oily products were purified by chromatography and their parity was attested by a single spot in TLC.

Solvolysis of the chloro-fluorocarbene adducts **1d** *and* **2d**

A soln of **1d** (41 mg, 0.10 mmol) and 0.020 ml triethylamine in 1.0 ml t-BuOH was heated at 110° (sealed tube) during 24 hr. After evaporation of the solvent the mixture was purified by prep TLC (silica, EtOAc/cyclohexane 1:1). **4d** was isolated (20 mg, 45%) as a brownish oil. IR: 1745, 1710, 1680, 1645 cm^{-1}; NMR δ 1.34, 1.55 (6H, 2×s, $C(CH_3)_2$), 2.07 (3H, s, OAc), 3.23 (3H, s, $N-CH_3$), 4.1–4.5 (3H, m, H-4', H-5'), 4.57–4.83 (2H, m, H-2', H-3'), 5.41 (1H, d×d, $J_{H,F}$ = 13, $J_{5,7}$ = 2, H-7), 5.51 (1H, d, J = 2, H-1'), 5.82 (1H, d×d, $J_{H,F}$ = 13, $J_{5,7}$ = 2, H-5). In the same way **2d** (41 mg) was converted into **4d**, yield 21 mg, (47%).

Solvolysis of the dibromocarbene adducts **1b** *and* **2b**

A soln of **2b** (57 mg, 0.10 mmol) and 0.020 ml triethylamine in 1.0 ml t-BuOH was heated at 110° (sealed tube) during 4 hr. After evaporation of the solvent the residue was purified by preparative TLC. In addition to an unidentified product (4 mg) **4b** (17 mg, 30%) and **6a** (6 mg, 11%) were isolated as slightly coloured oils.

4b: IR: 1750, 1700, 1670, 1640 cm^{-1}; NMR δ: 1.24 (9H, s, O-tBu), 1.33, 1.53 (6H, 2×s, $C(CH_3)_2$), 2.10 (3H, s, OAc), 3.26 (3H, s, $N-CH_3$), 4.3–4.5 (3H, m, H-4', H-5'), 4.7–4.9 (2H, m, H-2', H-3'), 5.32 (1H, d, J = 1.5, H-7), 5.59 (1H, d, H-1'), 6.51 (1H, d, J = 1.5, H-5).

6a: IR: 1740, 1720, 1700, 1680, 1620, NMR δ: 1.36, 1.59 (6H, 2×s, $C(CH_3)_2$), 2.12 (3H, s, OAc), 3.37 (3H, s, $N-CH_3$), 4.3–4.5 (3H, m, H-4', H-5'), 4.7–4.9 (2H, m, H-2', H-3'), 5.9 (1H, m, H-1'), 8.25 (1H, s, H-6), 10.05 (1H, s, CHO). In the same way **1b** produced **4b** (10%, contaminated with some starting material) and **6a** (13 mg, 31%).

Synthesis of dibromocarbene adducts **1c** and **2c**

A soln of 680 mg (2.41 mmol) 2',3' - isopropylidene - 3 - methyl - 5' - deoxyuridine[8a,b] and tribromomethylphenylmercury (3.85 g, 7.2 mmol) in 10 ml benzene was refluxed for 2 hr. The soln was filtered evaporated to dryness and the residue purified over a column (silica, EtOAc/cyclohexane 1:10 gradient to 1:3). In addition to some starting material (157 mg, 23%) the adducts **1c** and **2c** were isolated and purified by preparative TLC, yields **1c**: 111 mg (10%), **2c**: 61 mg (6%).

1c: IR: 1720, 1680 cm^{-1}; NMR δ: 1.37, 1.58 (6H, 2×s, $C(CH_3)_2$), 3.10 (3H, d, J = 10, H-5), 3.18 (3H, s, $N-CH_3$), 3.52 (1H, d, J = 10, H-6), 6.07 (1H, m, H-1').

2c: IR: 1720, 1680 cm^{-1}; NMR δ: 1.35, 1.56 (6H, 2×s, $C(CH_3)_2$), 3.02 (3H, d, J = 10, H-5), 3.15 (3H, s, $N-CH_3$), 3.52 (1H, d, J = 10, H-6), 5.67 (1H, m, H-1').

Sovolysis of the dibromocarbeneadducts **1c** *and* **2c**

A soln of **1c** (54 mg, 0.12 mmol) and 0.020 ml triethylamine in 1.0 ml t-BuOH was heated to 110° (sealed tube) during 4 hr. The solvent was evaporated and the residue purified by preparative TLC (silica; EtOAc/cyclohexane 1:3), resulting in **4c** (7 mg, 13%) and **6b** (7 mg, 19%) as brownish oils.

4c: IR: 1680, 1650, 1620 cm^{-1}. NMR δ: 5.31 (1H, d, J = 1.5, H-7), 5.50 (1H, d, J = 2, H-1') 6.44 (1H, d, J = 1.5, H-5).

6b: IR: 1720, 1690, 1660, 1600 cm^{-1}. NMR δ: 5.72 (1H, d, J = 2, H-1') 8.19 (1H, s, H-6), 10.05 (1H, s, CHO). Analogously **2c** (61 mg) produced **4c** (18 mg, 30%) and **6b** (3 mg, 7%).

Synthesis and solvolysis of dibromocarbene adduct **7a**

Reaction of 3-benzyl-1-benzyloxymethylene uracil with tribromomethylphenylmercury in refluxing benzene produced **7a** in 20% yield (recovered starting material: 60%). Solvolysis of **7a** (48 mg) in t-BuOH as described for **1c** produced **8a**: (6 mg, 13%) and **9** (4 mg, 12%). Recovered starting material: 12 mg (25%).

8a: IR: 1680, 1650, 1620 cm^{-1}. NMR δ: 6.62, 6.50 (2×H-5).

9: IR: 1720, 1690, 1660, 1600 cm^{-1}.

Synthesis and solvolysis of dibromocarbene adduct **7b**

With 1-(3-phenylpropyl)-3-methyluracil and tribromomethylphenylmercury in refluxing benzene **8b** was obtained in 56% yield (recovered starting material: 22%).

7b: NMR: 2.96 (1H, d, J = 9, H-5), 3.13 (3H, s, $N-CH_3$), 3.36 (1H, d, J = 9, H-6). Solvolysis of **7b** (50 mg) as described for **1c** produced **8b** (29 mg, 58%) and **10** (2.5 mg, 5%).

8b: IR: 1670, 1640, 1620 cm^{-1}. NMR δ: 1.16, 1.21 (2×s, t-butyl), 3.29, 3.32 (2×s, $N-CH_3$), 4.92, 5.66 (2×d, J = 1.5, H-7), 6.42, 6.49 (2×d, J = 1.5, H-5).

10: IR: 1780, 1720, 1650, 1630 cm^{-1}.

Solvolysis of the dichlorocarbene adducts **1a** *and* **2a**

A soln of **2a** (83 mg, 0.20 mmol), 0.020 ml MeOH (0.50 mmol) and 0.028 ml triethylamine in 10 ml benzene was heated to 125° (sealed tube) for 24 hr. The soln was filtered, the filtrate evaporated and the residue purified over TLC (silica, EtOAc/cyclohexane 1:1). Besides starting material (25 mg, 30%) **6a** (0.50 mg, 0.5%), **6a**-dimethylacetal (1.0 mg, 1%) and a mixture of C-7-epimers of **4a** (23 mg, 28%) were isolated. The isomers of **4a** were separated on TLC (silica, benzene/acetone 10:1).

4a: C-7 epimer in *syn*-conformation. IR: 1740, 1680, 1655, 1630 cm^{-1}. NMR: δ: 1.36, 1.58 (6H, 2×s, $C(CH_3)_2$), 2.10 (3H, s, OAc), 3.24 (3H, s, $N-CH_3$), 3.45 (3H, s, OCH_3), 4.31 (3H, m, H-4', H-5'), 4.80–4.97 (3H, m, H-2', H-3', H-7), 5.46 (1H, d, J = 2, H-1'), 6.33 (1H, d, J = 1.5, H-5).

4a: C-7 epimer in *anti*-conformation. IR: 1735, 1680, 1650, 1630 cm^{-1}. NMR δ: 1.36, 1.57 (6H, 2×s, $C(CH_3)_2$), 2.12 (3H, s, OAc), 3.27 (3H, s, $N-CH_3$), 3.39 (3H, s, OCH_3), 4.31 (3H, m, H-4', H-5'), 4.67 (2H, H-2', H-3'), 4.98 (1H, d, J = 1.5, H-7), 5.83 (1H, d, J = 2.5, H-1'), 6.38 (1H, d, J = 1.5, H-5).

6a: (dimethylacetal). IR: 1740–1720, 1670 cm^{-1}. NMR δ: 1.40, 1.62, (6H, 2×s, $C(CH_3)_2$), 2.14 (3H, s, OAc), 3.37 (3H, s, $N-CH_3$), 3.44, 3.46 (6*H*, 2×*s*, $C(OCH_3)_2$, 4.38 (3*H*, *m*, *H*-4', *H*-5'), 4.8–5.1 (2H, m, H-2', H-3'), 5.37 (1H, s, H-7), 5.78 (1H, d, J = 2, H-1'), 7.58 (1H, s, H-6). Solvolysis of **1a** produced both epimers of **4a** (13%, contaminated with starting material), **6a** (4%) and **6a** dimethylacetal (2%).

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[6]A small amount of the dimethylacetal of **6a** was also obtained in the reaction of methanol with **1a** and **2a**.

[7]This mechanism is favoured in the case of the nucleoside

adducts in view of the possible participation of the ether oxygen of the ribose (**11**, Scheme 3). A mechanism involving a C_6–C_7 bond cleavage following nucleophilic attack by a molecule of methanol (Ref. 1) cannot, however, be excluded. In the latter case a loss of methanol and hydrolysis will have to be invoked to account for the formation of **6**.

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