Aziridination of the Uracil 5,6-Olefinic Bond of 3-*N*-3′,5′-Di-*O*-tribenzoyl-5-vinyl-2′-deoxyuridine

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Oxidation of *N*-aminophthalimide with lead tetra-acetate at −50° gives *N*-acetoxyaminophthalimide (**3**) which selectively aziridinates the 5,6-double bond present in 3-*N*-3′,5′-di-*O*-tribenzoyl-5-vinyl-2′-deoxyuridine (**1a**) to yield 2-[1′-(2′-deoxy-β-D-ribofuranosyl)]-7-(1-phthalimido)-4-*N*-3′,5′-di-*O*-tribenzoyl-6-vinyl-2,4,7-triazabicyclo[4.1.0]heptan-3,5-dione (**5**).

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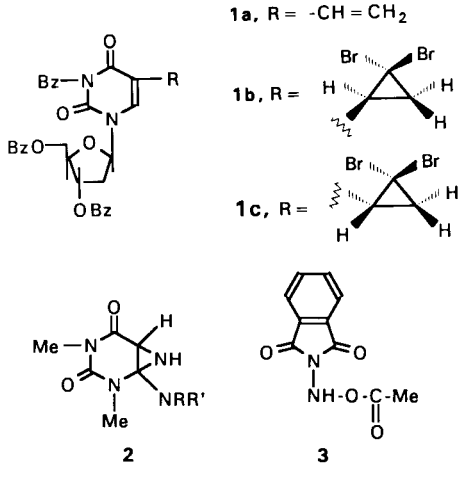
Introduction.

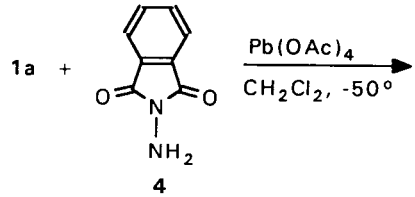
The development of new methods for pyrimidine nucleoside modification is currently of great interest. Thus, the cycloaddition of dibromocarbene to 3-*N*-3′,5′-di-*O*-tribenzoyl-5-vinyl-2′-deoxyuridine (**1a**) afforded a mixture of the two diastereomers 5-[(1*S*)-2,2-dibromocyclopropyl]- (**1b**) and 5-[(1*R*)-2,2-dibromocyclopropyl]-3-*N*-3′,5′-di-*O*-tribenzoyl-2′-deoxyuridine (**1c**) in a ratio of 1:1 [1]. The 5,6-double bond of uracil analogues can undergo a variety of photochemical reactions since photolysis of 6-azido-1,3-dimethyluracil with amines gave rise to 6-alkylamino-5-amino-1,3-dimethyluracils *via* an aziridine intermediate **2** [2]. The observation [3] that oxidation of *N*-aminophthalimide with lead tetra-acetate at low temperature gives *N*-acetoxyaminophthalimide (**3**) which aziridinates olefins prompted us to investigate the reaction of **3** with 3-*N*-3′,5′-di-*O*-tribenzoyl-5-vinyl-2′-deoxyuridine (**1a**) which could add to the 5-vinyl substituent and/or the 5,6-uracil olefinic bond. We now report the synthesis of the novel bicyclic aziridine compound 2-[1′-(2′-deoxy-β-D-ribofuranosyl)]-7-(1-phthalinido)-4-*N*-3′,5′-di-*O*-tribenzoyl-6-vinyl-2,4,7-triazabicyclo[4.1.0]heptan-3,5-dione (**5**).

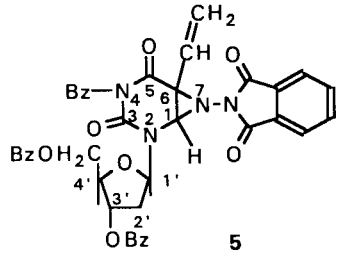


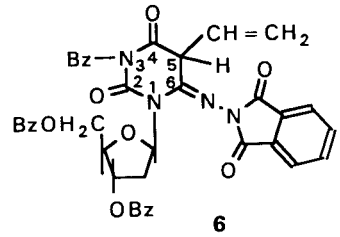
Chemistry.

The reaction of *N*-acetoxyaminophthalimide (**3**), prepared *in situ* by oxidation of *N*-aminophthalimide (**4**) with lead tetra-acetate in dry dichloromethane at -50°, with 3-*N*-3′,5′-di-*O*-tribenzoyl-5-vinyl-2′-deoxyuridine (**1a**) afforded 2-[1′-(2′-deoxy-β-D-ribofuranosyl)]-7-(1-phthalimido)-4-*N*-3′,5′-di-*O*-tribenzoyl-6-vinyl-2,4,7-triazabicyclo-[4.1.0]heptan-3,5-dione (**5**) in 42% yield as illustrated in Scheme 1. The reaction of **3** with **1a** was regiospecific since no product arising from aziridination of the 5-vinyl substituent of **1a** was obtained. It appears that the 5-vinyl substituent present in **1a** is essential since similar reactions employing 3′,5′-di-*O*-acetyl-3-*N*-benzoyl-2′-deoxyuridine possessing either a C-5 hydrogen or C-5 methyl substituent resulted in recovery of the parent unreacted 2′-deoxyuridine.

Scheme 1





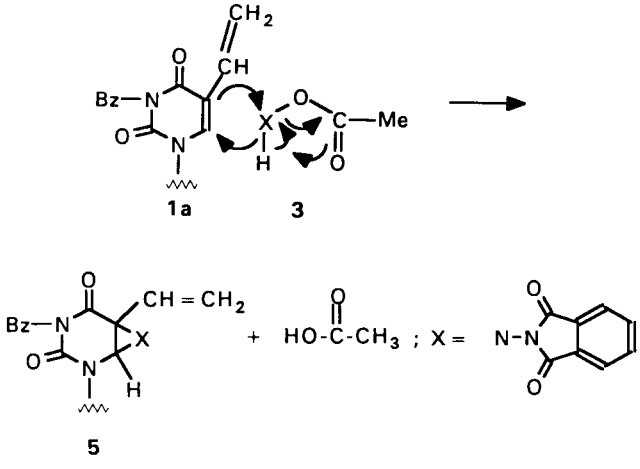


The structure of 2-[1′-(2′-deoxy-β-D-ribofuranosyl)]-7-(1-phthalimido)-4-*N*-3′,5′-di-*O*-tribenzoyl-6-vinyl-2,4,7-triazabicyclo[4.1.0]heptan-3,5-dione (**5**) was confirmed using ^{1}H nmr and ^{13}C nmr experiments. Selective irradiation of the

H-1 proton resonance, which appeared as a singlet at δ 6.2, confirmed the assignment of the C-1 resonance at δ 52.91 in the ^{13}C nmr spectrum. This result rules out the isomeric structure **6**, which could result from opening of the aziridine ring present in **5**, since the C-6 $C=N$ resonance for **6** would be expected to appear in the δ 140-160 range. Furthermore, selective excitation of the H-1 proton resonance at δ 6.2 and acquistion of an INAPT [4] spectrum showed that the C-1 proton present in **5** is coupled to the C-1', $-CH=CH_2$, C-3 $C=O$ and C-5 $C=O$ atoms.

The mechanism by which **3** aziridinates the 5,6-olefinic bond of **1a** may resemble the mechanism for epoxidation of olefins by peracids as illustrated below in Scheme 2 [5].

Scheme 2



Removal of the phthalimido group by cleavage of the N-N bond in **5** was attempted by treatment with caesium fluoride in dimethylformamide or tetra-*n*-butylammonium fluoride in tetrahydrofuran at 25°. Both reactions were unsuccessful since none of the desired product could be isolated from the many products formed, which is likely due to the lability of the aziridine ring.

EXPERIMENTAL

Nuclear magnetic resonance spectra (^1H nmr, ^{13}C nmr) were determined for solutions in deuteriochloroform with TMS as an internal standard (^1H nmr) with a Bruker AM-300 spectrometer. Positive ion fast atom bombardment (FAB) mass spectra were obtained using an AEI MS-9 mass spectrometer. Silica gel column chromatography was carried out using Merck 7734 silica gel (100-200 μ partical size). Dichloromethane was distilled from calcium hydride prior to use. 3-*N*-3',5'-Di-*O*-tribenzoyl-5-vinyl-2'-deoxyuridine (**1a**) was prepared according to the literature procedure [1].

2-[1'-(2'-Deoxy-β-D-ribofuranosyl)]-7-(1-phthalimido)-4-*N*-3',5'-di-*O*-tribenzoyl-6-vinyl-2,4,7-triazabicyclo[4.1.0]heptan-3,5-dione (**5**).

Lead tetra-acetate (50 mg, 0.1 mmole) was added to a suspension of *N*-aminophthalimide (16 mg, 0.1 mmole) in dry dichloromethane (5 ml) at -50° and the mixture was stirred for 15 minutes. 3-*N*-3',5'-Di-*O*-tribenzoyl-5-vinyl-2'-deoxyuridine (56 mg, 0.1 mmole) was then added with stirring and the reaction mixture was allowed to warm to 25°. The insoluble material was filtered off and the filtrate was washed successively with saturated aqueous sodium hydrogen carbonate (5 ml) and water (2 x 5 ml). The solution was dried (sodium sulfate) and the solvent was removed *in vacuo* to give a residue which was purified by elution from a silica gel column using ethyl acetate-hexane (30:70, v/v) as eluent to yield **5** as a viscous oil (30 mg, 42%); ^1H nmr (deuteriochloroform): δ 2.54 (dd, J_{gem} = 14.2, $J_{1',2''}$ = 4.8 Hz, 1H, H-2''), 3.35 (ddd, J_{gem} = 14.2, $J_{1',2'}$ = 8.7, $J_{2',3'}$ = 6.0 Hz, 1H, H-2'), 4.58 (ddd, $J_{4',5'}$ = 7.2, $J_{4',5''}$ = 4.5, $J_{3',4'}$ = 2.1 Hz, 1H, H-4'), 4.76 (dd, J_{gem} = 11.4, $J_{4',5''}$ = 4.5 Hz, 1H, H-5''), 5.22 (dd, J_{gem} = 11.4, $J_{4',5'}$ = 7.2 Hz, 1H, H-5'), 5.56 (d, J_{cis} = 10.3 Hz, 1H, CH = C*H*H'), 5.60 (d, J_{trans} = 18.2 Hz, 1H, CH = CH*H'*), 5.76 (dd, $J_{2',3'}$ = 6.0, $J_{3',4'}$ = 2.1 Hz, 1H, H-3'), 6.2 (s, 1H, H-1), 6.40 (dd, J_{trans} = 18.2, J_{cis} = 10.3 Hz, 1H, $-CH=CH_2$), 6.55 (dd, $J_{1',2'}$ = 8.7, $J_{1',2''}$ = 4.8 Hz, 1H, H-1'), 7.36-8.20 (m, 19H, aryl hydrogens); ^{13}C nmr (deuteriochloroform): δ 34.82 (C-2'), 51.05 (C-6), 52.91 (C-1), 64.11 (C-5'), 74.76 (C-3'), 82.31 (C-4'), 85.35 (C-1'), 122.57 ($CH=CH_2$), 129.53 ($CH=CH_2$), 148.73 (C-3 $C=O$), 164.04 (C-5 $C=O$), 164.72 (phthalimido $C=O$), 165.79, 166.34 and 167.33 (two $PhCO_2$, PhCON); positive ion FAB ms: m/z 727.14 (M + 1, 0.18%).

Anal. Calcd. for $C_{40}H_{30}N_4O_{10}$: C, 66.10; H, 4.16; N, 7.71. Found: C, 65.80; H, 4.38; N, 7.36.

Acknowledgments.

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