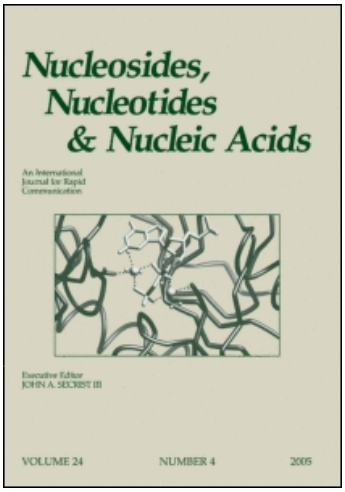

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Synthesis of 2'-C-Nitromethyl Derivatives of Uridine and the Structure of a Carbon-Bridged Cyclonucleoside Derived Therefrom (Nucleosides and Nucleotides 51)

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SYNTHESIS OF 2'-C-NITROMETHYL DERIVATIVES OF URIDINE AND THE STRUCTURE OF A CARBON-BRIDGED CYCLONUCLEOSIDE DERIVED THEREFROM (NUCLEOSIDES AND NUCLEOTIDES 51[1]).

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ABSTRACT

Treatment of a 2'-ketouridine with a nitromethyl carbanion afforded a 2'-C-nitromethyl derivative which was deprotected to give 2'-C-nitromethyl-ß-D-arabinosyluracil. A 2'-C-nitromethylarabinosyl-5-bromouracil was converted to a carbon-bridged cyclonucleoside through the 2'-nitromethylene derivative by treatment with sodium borohydride and DBU. A mechanism for this conversion was presented.

To expand our studies on the synthesis of carbon-bridged cyclonucleosides and their phosphates[2] as probes for stereochemical studies of substrates and enzymes utilizing them, the branched chain sugar nucleosides seem to be suitable intermediates provided that these are readily accessible. There have been several reports on the synthesis of branched chain sugar nucleosides of biological interest. Most of the synthetic procedures involve the condensation of a base moiety and a preformed branched chain sugar[3,4]. It seems likely that the ketosugar nucleosides should be useful starting nucleosides for the introduction of carbon units. One brief report described the addition of nitromethyl carbanion to a 2'-keto derivative of xylofuranosyladenine to give the 2'-C-nitromethyl derivative[4]. It has been generally recognized that the 2'-ketonucleosides are very unstable in alkaline conditions[5]. Therefore, despite successful synthesis of 2'-keto-uridines and -cytidines by Moffatt and co-workers, there has been no report on the addition of nucleophiles to

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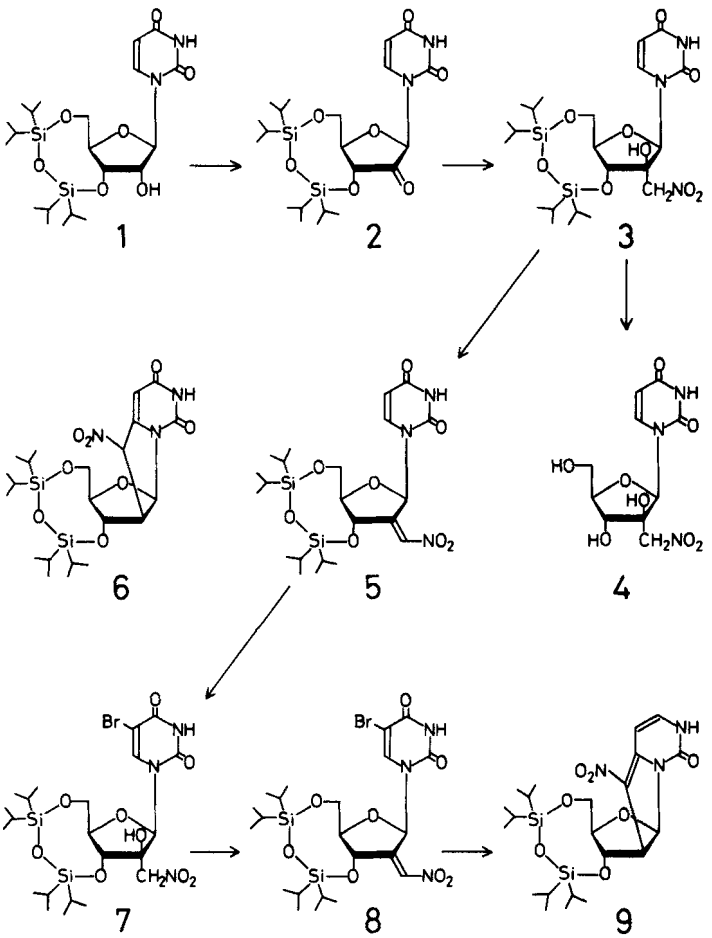
the 2'-keto function except by borohydride reduction[6]. We have recently found that a 2'-ketouridine underwent the Wittig reaction rather smoothly to give the 2'-methylene nucleosides[7]. This paper describes the reaction of a 2'-ketouridine with a nitromethyl carbanion and the conversion of the product to a carbon-bridged cyclopyrimidine nucleoside.

Treatment of 3',5'-O-(tetraisopropyldisiloxane-1,3-diyl) uridine[8] (1) with dicyclohexylcarbodiimide (DCC) and dimethylsulfoxide (DMSO) in the presence of trifluoroacetic acid afforded the 2'-ketouridine (2) in crystalline form[9]. Treatment of 2 with sodium hydride and nitromethane in tetrahydrofuran (THF) at room temperature afforded, after preparative thin layer chromatography, a single crystalline product (3). The structure of 3 was confirmed by the mass and NMR spectra, the latter showing the 2''-protons at 4.93 and 4.67 ppm with a vicinal coupling constant of 14.4 Hz. The stereochemistry at the 2'-position of 3 was not determined at this stage but it was conceivable that the nucleophilic attack should have occurred from the less hindered bottom side to give the 2'(S)-diastereomer. Deprotection of 3 with tetra-n-butylammonium fluoride gave the free nucleoside (4). Compound 4 migrated in a paper electrophoretic system with a solvent containing boric acid similarly as did arabinofuranosyluracil and unlike uridine, which means that the configuration of the 2',3'-diol system was trans. Therefore the structure of 4 must be 2'-C-nitromethyl-ß-D-arabinofuranosyluracil. In order to construct a carbon bridge between C-6 and C-2' in 4 the configuration at the 2'-position should be altered. Treatment of 3 with acetic anhdride in DMSO resulted in a dehydration to afford a single 2'-C-nitromethylene derivative (5) as a foam. Although the geometry at the 2''-position was undetermined, the presence of the 2'-2'' methylene function was confirmed by the NMR measurement. The allyl couplings between H-1' and H-2'', and H-2'' and H-3', and a long range coupling between H-1' and H-3' were observed.

Treatment of 5 with sodium borohydride did not give the initially anticipated 2'-C-nitromethyl derivative and the



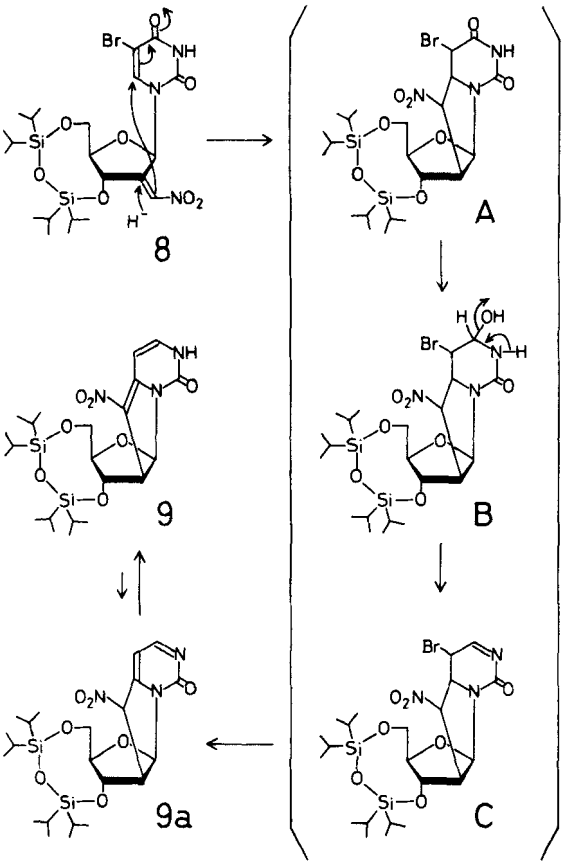
Scheme 1

product has lost the UV absorption for the uracil moiety. Although the compound was not isolated and fully characterized, it was conceivable that there had been a cyclization between the C-2'' and C-6 in 5 caused by the hydride treatment. Similar cyclization had been reported in the Michael reaction of a 5'-Nitromethyleneuridine[10]. Therefore one could expect that if the 5-halogeno function was present in 5 the same reaction would preceed to give the 6,2'-cyclouridine derivative (6). Thus compound 3 was reacted with bromine in acetic acid to give the 5-bromouridine (7) as a foam which was then treated with acetic anhdride in DMSO to furnish the 2'-exomethylene derivative (8). Treatment of 8 with sodium borohydride in

ethanol afforded a product which had again no UV absorption of the uracil moiety. The crude product was further treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene and the product was isolated after preparative thin layer chromatography as a yellow foam (9). Mass spectra of 9 gave the fragment ion of 468 (molecular ion - isopropyl). The UV spectra (λmax, 415 and 397 nm) showed an enormous red shift. NMR spectra showed the presence of six protons for the sugar portion with two base protons coupled to each other and an exchangeable proton coupled with a base proton. These features are best explained by the structure 9, a dihydropyrrolo[1,5-c] pyrimidinone. The product 9 would probably be derived by the sequence shown in chart 2. The reaction would be initiated by hydride attack from the borohydride on the 2'-carbon of 8 to generate the 2''-nitromethyl anion which immediately added to the 6-position to give the cyclodihydro intermediate (A). Instead of dehydrobromination of A to give the anticipated product 6, the reduction of the 4-carbonyl group of A by the hydride occurred to give B, which was dehydrated to give intermediate (C). It has been demonstrated[11] that the borohydride treatment of 5,6-dihydrouridine gave rise to the ureidopropanol derivative by the reduction of the 4-carbonyl, ring opening and further reduction of the aldehyde. In the present case the presence of the 6,2'-cyclo linkage in A would have prevented the ring opening at the initial reduction stage B, and the dehydration must have proceeded to give the intermediate C. Action of DBU to C promoted the dehydrobromination to furnish the product 9a which tautomerized to the more stable product 9. It is reasonable to expect that the red shift of the UV spectra of 9 would be due to the conjugation of the nitro group with the base moiety of 9. In the structure 9a, a 6-alkyl-2-pyrimidinone, such a red shift would not be expected.

EXPERIMENTAL

General procedures---- Melting points were determined on a Yanagimoto micromelting point apparatus (MP-3) and



Scheme 2

were uncorrected. The ^{1}H-NMR spectra were recorded with a JEOL FX100-FT or FX200-FT spectrometer with tetramethylsilane as internal standard. Chemical shifts were reported in ppm (δ), and signals were described as s (singlet), d (doublet), t (triplet), m (multiplet), or br (broad). All exchangeable protons were confirmed by addition of D_2O. UV spectra were recorded with a Shimadzu UV-240 spectrophotometer and IR spectra with Hitachi 215 spectrophotometer. Mass spectra (MS) were measured on a JEOL JMS D-300 spectrometer. Thin layer chromatography was carried out on Merck precoated plate $60F_{254}$. Silica gel for column chromatography was from Wako Co., C-200.

2'-Keto-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)uridine (2)---- Compound 1 (7.17 g) was dissolved in a mixture of 80 mL of DMSO and 70 mL of benzene. To the solution was

added DCC (9.14 g), pyridine (1.13 mL) and trifluoroacetic acid (0.565 mL) and the mixture was stirred for 24 h at room temperature. The solution was mixed with 100 mL of $CHCl_3$ and 100 mL of H_2O under stirring for 10 min and insoluble material was filtered off. The organic layer was separated, the aqueous layer was extracted with $CHCl_3$, and the combined extract was treated with 7.0 g of oxalic acid for 15 min under stirring. The insoluble material was removed by filtration and the filtrate was evaporated to dryness. The residue was extracted with $CHCl_3$. The $CHCl_3$ was evaporated and the residue was crystallized from n-hexane to give 5.10 g (71%) of 2, mp 155-158°. Ms (m/z): 484 (M^+), 441 $(M\text{-iPr})^+$. NMR (200 mHz, $CDCl_3$): 8.72 (br, 1, H-N^3), 7.12 (d, 1, H-6, J= 8.2 Hz), 5.75 (dd, 1, H-5, J_{5,N^3}= 2.2 Hz), 5.04 (d, 1, H-3', $J_{3',4'}$= 9.3 Hz), 4.99 (s, 1, H-1'), 4.13 (d, 2, H-5', $J_{4',5'}$= 3.9 Hz), 3.95 (m, 1, H-4'), 1.09 (m, 28, iPr). Anal. Calcd for $C_{21}H_{36}N_2O_7Si_2$: C, 52.04; H, 7.49; N, 5.78. Found: C, 52.03, H, 7.53; N, 5.74.

1-[2-Nitromethyl-3,5-O-(tetraisopropyldisiloxane-1,3-diyl)-ß-D-arabinofuranosyl]uracil (3)---- Compound 2 (0.25 g) was dissolved in a mixture of THF (5 mL) and nitromethane (5 mL), and 41 mg of 60% NaH was added to the mixture. After stirring for 2 h the solution was neutralized with 1 N HCl and concentrated to dryness. The residue was partitioned with $CHCl_3$ and H_2O, and the organic layer was applied to a preparative tlc plate and developed with AcOEt-$CHCl_3$ (1:2). The appropriate band was extracted with the same solvent and the product was crystallized from MeOH to give 0.24 g (84%) of 3, mp 129-131°. Ms (m/z): 502 $(M\text{-iPr})^+$. NMR (100 mHz, $CDCl_3$): 9.77 (br, 1, H-N^3), 7.61 (d, 1, H-6, J= 9.1 Hz), 6.01 (s, 1, H-1'), 5.69 (d, 1, H-5), 4.93 (d, 1, H-2''a), 4.67 (d, 1, H-2''b, $J_{a,b}$= 14.4 Hz), 4.57 (s, 1, HO), 4.47 (d, 1, H-3', J= 5.4 Hz), 4.03 (br, 2, H-5'), 3.85 (m, 1, H-4'), 1.10 (m, 28, iPr). Anal. Calcd for $C_{22}H_{39}N_3O_9Si_2$: C, 48.42; H, 7.20; N, 7.70. Found: C, 48.61; H, 7.32; N, 7.79.

1-(2-Nitromethyl-ß-D-arabinofuranosyl)uracil (4)---- Compound 3 (83 mg) was dissolved in 1 N tatra-n-butylammo-

nium fluoride in THF (1 mL) and the solution was stirred for 1 h. After concentration of the solvent the residue was applied to a preparative tlc plate and developed with $CHCl_3$-MeOH (7:1). The appropriate band was extracted with $CHCl_3$-EtOH (1:1) and the product was crystallized from MeOH to give 39 mg (85%) of 4, mp 223-224°. Migrated distance in paper elctrophoresis (600 v, 15-20 mA, 35 min in 0.9 M sodium borate, pH 7.5): 4.2 cm; arabinofuranosyluracil: 4.1 cm; uridine: 5.4 cm; uridine 2',3'-cyclic phosphate: 5.7 cm; uridine 2'(3')-phosphate: 6.2 cm. (0.05 M sodium acetate, pH 5.0): 3.0 cm; uridine: 3.3 cm; uridine 2',3'-cyclic phosphate: 6.6 cm; uridine 2'(3')-phosphate: 6.4 cm; arabinofuranosyluracil: 3.2 cm. NMR (100 mHz, DMSO-d_6-D_2O): 7.59 (d, 1, H-6, J= 8.1 Hz), 5.95 (s, 1, H-1'), 5.62 (d, 1, H-5), 4.93 (d, 1, H-2''a), 4.58 (d, 1, H-2''b, $J_{a.b}$= 13.8 Hz), 4.12 (d, 1, H-3', J= 1.7 Hz), 3.94 (dd, 1, H-4'), 3.63 (d, 2, H-5', J= 6.0 Hz). Anal. Calcd for $C_{10}H_{13}N_3O_8$: C, 39.61; H, 4.32; N, 13.86. Found: C, 39.46; H, 4.39; N, 13.70. Ms (m/z): 242 $(M-CH_3NO_2)^+$, 112 $(B+1)^+$.

1-[2-Nitromethyl-3,5-O-(tetraisopropyldisiloxane-1,3-diyl)-ß-D-arabinofuranosyl]-5-bromouracil (7)---- Compound 3 (0.5 g) and sodium acetate (0.227 g) were dissolved in 10 mL of AcOH, the solution was cooled in an ice bath, and Br_2 (52 uL) was added to the solution. The solution was stirred overnight at room temperature and the solvent was removed in vacuo and the residue was taken up in 20 mL of benzene and refluxed for 20 min. The solvent was evaporated and the residue was applied to a column of silica gel. Elution was performed with AcOEt-$CHCl_3$ (1:1) and the eluate was concentrated to leave 7 (0.17 g, 60%) as a foam. UV λ_{max}^{MeOH}: 275 nm. Ms (m/z): 581, 579 $(M-iPr)^+$. NMR (100 mHz, $CDCl_3$): 9.44 (br, 1, H-N^3), 7.85 (s, 1, H-6), 5.95 (s, 1, H-1'), 4.90 (d, 1, H-2''a), 4.65 (d, 1, H-2''b, $J_{a,b}$= 14.4 Hz), 4.43 (br, 2, HO and H-3'), 4.09 (d, 2, H-5'), 3.97 (m, 1, H-4'), 1.10 (m, 28, iPr).

2'-Deoxy-2'-nitromethylene-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-5-bromouridine (8)---- Compound 7 (100

mg), was dissolved in 1.8 mL of Ac_2O and 0.2 mL of DMSO, and the solution was stirred at 30° for 2 days. The mixture was partitioned with 15 mL of $CHCl_3$ and 15 mL of H_2O , and the organic layer was concentrated and the residue was applied to a preparative tlc plate (AcOEt-$CHCl_3$, 1:6). The appropriate band was extracted with the same solvent and the solvent was removed to leave 56 mg (58%) of 8 as a foam. UV λ_{max}^{MeOH}: 276 nm. Ms (m/z): 564, 562 $(M\text{-}iPr)^+$. NMR (100 mHz, $CDCl_3$): 8.14 (br, 1, H-N^3), 7.63 (s, 1, H-6), 7.10 (dd, 1, H-1', J= 2.4 and 2.2 Hz), 6.41 (dd, 1, H-2'', J= 1.7 and 2.4 Hz), 5.56 (dt, 1, H-3', J= 8.5 Hz), 4.11 (br, 2, H-5'), 3.71 (m, 1, H-4'), 1.10 (m, 28, iPr).

1-[2'-Deoxy-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-6,2'-nitromethano-ß-D-ribofuranosyl]-2-pyrimidinone (9)---- Compound 8 (50 mg) was dissolved in 2 mL of abs.EtOH to which was added 10 mg of $NaBH_4$ and the solution was stirred for 20 min at room teperature. After neutralization of the solution with 1 N AcOH the solvent was removed and the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was concentrated and the residue was dried overnight and then was taken up in 2 mL of benzene. DBU (20 uL) was added and the solution was stirred at 60° for 20 min. After neutralization with AcOH-benzene, the solvent was removed and the residue was applied to a preparative tlc plate ($CHCl_3$-MeOH, 9:1). The appropriate band was eluted with $CHCl_3$AcOEt (1:1) and the solvent was evaporated to leave a yellow foam of 9 (21 mg, 51%). UV λ_{max}^{MeOH}: 415, 397 nm. $\lambda_{max}^{MeONa\text{-}MeOH}$: 412 nm. Ms (m/z): 468 $(M\text{-}iPr)^+$. NMR (200 mHz, $CDCl_3$): 9.89 (d, 1, H-N^3, $J_{3,4}$= 5.6 Hz), 7.16 (dd, 1, H-4, $J_{4,5}$= 7.8 Hz, converted to a doublet by addition of D_2O), 6.98 (d, 1, H-5), 6.23 (d, 1, H-1', $J_{1',2'}$= 7.4 Hz), 4.71 (dd, 1, H-3', $J_{2',3'}$= 2 Hz, $J_{3',4'}$= 4 Hz), 4.17 (m, 2, H-5'), 4.02 (dd, 1, H-2'), 3.57 (dt, 1, H-4', $J_{4',5'}$= 8.3 Hz), 1.10 (m, 28, iPr).

REFERENCES AND NOTES

1. T. Ueda, H. Usui, S. Shuto, and H. Inoue, Chem. Pharm. Bull., 32, in press (1984).

2. a) A. Matsuda, K. Muneyama, T. Nishida, T. Sato, and T. Ueda, Nucleic Acids Res., 3, 3349 (1976). b) A. Matsuda, M. Tezuka, and T. Ueda, Tetrahedron, 34, 2449 (1978). c) A. Matsuda, M. Tezuka, K. Niizuma, E. Sugiyama, and T. Ueda, Tetrahderon, 34, 2633 (1978). d) A. Matsuda, K. Niizuma, and T. Ueda, Chem. Pharm. Bull., 28, 876 (1980). e) A. Matsuda and T. Ueda, Nippon Kagaku Kaishi, 845 (1981). f) T. Ueda and S. Shuto, Heterocycles, 17, 95 (1982).

3. For example see: a) H. P. Albrecht and J. G. Moffatt, Tetrahderon Letters, 1063 (1970). b) A. J. Brink, O. G. de Villieres, and A. Jordaan, J. Chem. Soc. Perkin I, 1068 (1977). c) J. M. J. Tronchet and J. F. Tronchet, Helv. Chim. Acta, 64, 425 (1981). d) A. Rosenthal and D. A. Baker, J. Org. Chem., 38, 198 (1973).

4. A. Rosenthal, M. Sprinzl, and D. A. Baker, Tetrahedron Letters, 4233 (1970).

5. J. G. Moffatt, in "Nucleoside Analogues: Chemistry, Biology, and Medical Applications", R. T. Walker, E. De Clercq, and F. Eckstein, Eds. Plenum Press, New York, 1979, pp. 71-164.

6. A. F. Cook and J. G. Moffatt, J. Am. Chem. Soc., 89, 2696 (1967) and U. Brodebeck and J. G. Moffatt, J. Org. Chem., 35, 2522 (1970).

7. T. Ueda, S. Shuto, T. Sano, H. Usui, and H. Inoue, Nucleic Acids Res. Symposium Series, No. 11, 5, (1982).

8. W. T. Markiewicz, J. Chem. Res. (S), 24 (1979).

9. a) Oxidation of 1 with oxalyl chloride and DMSO[9b] gave also 2 in better yield; T. Sano, H. Inoue, and T. Ueda, unpublished experiment. b) K. Onuma and D. Swern, Tetrahedron, 34, 1651 (1978). c) After completion of our work, a procedure for the synthesis of 2' and 3'-ketonucleosides by oxidation with chromium trioxide/acetic anhydride/pyridine was reported: F. Hansske and M. J. Robins, Tetrahedron Letters, 24, 1589 (1983). d) Synthesis of 2' and 3'-ketoadenosines were prepared in the free forms: R. P. Crews and D. C. Baker, Nucleosides and Nucleotides, 2, 275 (1983).

10. G. H. Jones and J. G. Moffatt, J. Carbohydr. Nucleosides, Nucleotides, 6, 127 (1979).
11. a) P. Cerutti, K. Ikeda, and B. Witkop, J. Am. Chem. Soc., 87, 2505 (1965). b) P. Cerutti, Y. Kondo, W. R. Landis, and B. Witkop, J. Am. Chem. Soc., 90, 771 (1968).

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