NOTES

Conversion of uridine 2′,3′-carbonates to anhydrouridines

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Uridine 2′,3′-carbonates are readily converted to 2,2′-anhydrouridines in hot dimethyl formamide with base catalysis. 3′,5′-Di-*O*-trityluridine is converted to 3′,5′-di-*O*-trityl-2,2′-anyhdro-1-β-D-arabinofuranosyluracil with diphenyl carbonate in the presence of sodium bicarbonate in hot dimethyl formamide.

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In a recent publication, Hampton and Nichol (1) reported the formation of 2,2′-anhydro-1-β-D-arabinofuranosyluracil (**2***a*) when uridine (**1***a*) was treated with diphenyl carbonate and sodium bicarbonate in hot *N*,*N*-dimethyl formamide (DMF). Replacement of uridine by other ribonucleosides in this reaction yielded 2′,3′-cyclic carbonates. These authors suggested that either uridine 2′,3′-carbonate (**3***a*) or 2′-phenoxycarbonyluridine (**4***a*) was probably the intermediate in the reaction (1). In an analogous case Ruyle *et al.* (2) found that 5′-*O*-trityluridine 2′,3′-thionocarbonate was readily converted to 5′-*O*-trityl-2,2′-anhydro-1-β-D-arabinofuranosyluracil when heated with imadazole in toluene. Since uridine 2′,3′-carbonates (**3***a*, *b*) were readily available as a result of another study (3) it was of interest to us to test them under the reaction conditions used by Hampton and Nichol.

As expected we found that both uridine 2′,3′-carbonate (**3***a*) and 5′-*O*-trityluridine 2′,3′-carbonate were readily converted to the anhydrouridines **2***a* and **2***b* respectively when heated in DMF with sodium bicarbonate or sodium carbonate. The cyclic carbonates were not converted to their anhydroforms when heated alone in DMF or in DMF containing phenol.

For comparison we obtained 3′,5′-di-*O*-trityluridine (**1***c*) and 2′,5′-di-*O*-trityluridine by a variation of the procedure of Yung and Fox (4) and subjected them to the diphenyl carbonate reaction of Hampton and Nichol. The 3′,5′-di-*O*-trityluridine was smoothly converted to 3′,5′-di-*O*-trityl-2,2′-anhydro-1-β-D-arabinofuranosyluracil (**2***c*) when heated with diphenylcarbonate and sodium bicarbonate in DMF. However 2′,5′-di-*O*-trityluridine was not converted to the 2,3′-anhydrouridine analogue under these conditions, but gave instead a good yield of 2′,5′-di-*O*-trityl-3′-*O*-phenoxycarbonyluridine. This result was not unexpected in view of previous observations (5) that 2,2′-anhydrouridines form much more readily than 2,3′-anhydrouridines.

These results confirm that uridine 2′,3′-carbonates **3***a* and **3***b* are probable intermediates in the conversion of uridine derivatives **1***a* and **1***b* to their anhydroforms using diphenyl carbonate in dimethyl formamide with base catalysis. However, when the 3′-position is blocked (**1***c*) other intermediates, most likely **4***c*, must occur.

Experimental

Materials

Thin-layer chromatography was carried out on Eastman Chromagram Sheets 6060 by the ascending technique. Thick-layer chromatography was carried out on glass plates (15 × 20 cm) coated with a 2 mm thick layer of silica gel DSF-5 (Mondray Chemicals Ltd.). Elemental analysis were performed by MicroTech Laboratories, Skokie, Illinois.

Melting points were obtained on a Fisher–Johns melting point apparatus and are reported uncorrected.

Uridine 2′,3′-carbonate (m.p. 122–126 °C) and 5′-*O*-trityluridine 2′,3′-carbonate (m.p. 134–135 °C) were prepared as previously described (3).

3′,5′-Di-*O*-trityluridine was prepared from uridine by the method of Yung and Fox (4). The isolation procedure was modified in that the 3′,5′- and 2′,5′-ditrityl mixture produced was separated by thick-layer chromatography using ether as developing agent. 2′,5′-Di-*O*-trityluridine (m.p. 216–218 °C) traveled fastest (R_f 0.76) while the 3′,5′-di-*O*-trityluridine (m.p. 134–138 °C) had an R_f value of 0.63 in ether.

5′-*O*-Trityluridine (m.p. 115–117 °C) was prepared by the procedure of Lohrman and Khorana (6).

2,2′-Anhydro-β-D-arabinofuranosyluracil (anhydrouridine m.p. 245–247 °C) was obtained from uridine by the

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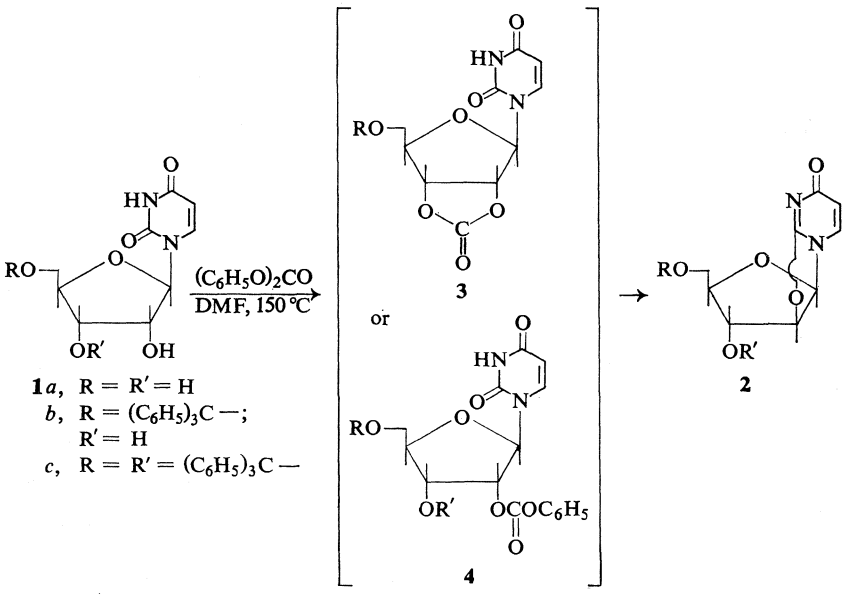

1*a*, R = R′ = H
b, R = $(C_6H_5)_3C-$; R′ = H
c, R = R′ = $(C_6H_5)_3C-$

method of Hampton and Nichol (1); the ultraviolet spectrum in 95% ethanol had λ_{max} 248 mμ (ε 8680), and λ_{max} 224 mμ (ε 10 600) and λ_{min} 236.5 mμ (ε 7560) and λ_{min} 210 mμ (ε 7130).

5′-O-Trityl-2,2′-anhydro-1-β-D-arabinofuranosyluracil (2b) from 5′-O-Trityluridine

5′-*O*-Trityluridine (0.67 g, 1.37 mmole) and diphenyl carbonate (0.39 g, 1.8 mmole) were dissolved in dimethyl formamide (1.5 ml). Sodium bicarbonate (0.01 g) was added and the mixture was heated at 150 °C for 30 min, cooled to room temperature and poured onto ether. A gummy precipitate formed and was collected and recrystallized from ethanol to yield 0.40 g (62%) of **2***b*, m.p. 218–220 °C (7), infrared spectrum (KBr disk): 6.15, 6.6, 6.8, and 14.2 μ; ultraviolet spectrum (95% ethanol): λ_{max} 249 mμ (ε 6630) and 224 mμ (sh); thin-layer R_f values were 0.70 (ethanol) and 0.55 (tetrahydrofuran). The product was identical to a sample prepared by the reaction of anhydrouridine (**2***a*) with trityl chloride in pyridine at room temperature.

Reactions of Uridine 2′,3′-carbonates in Dimethyl Formamide at 150 °C

(a) 5′-*O*-Trityluridine 2′,3′-carbonate (**3***b*, 204 mg, 0.4 mmole) was heated with diphenyl carbonate (114 mg, 0.64 mmole) and sodium bicarbonate (25 mg) in dimethyl formamide (0.2 ml) at 150 °C for 30 min. The solution was cooled and upon addition of ether a gummy precipitate formed which was collected and crystallized from ethanol to yield 110 mg (59%) of 5′-*O*-tritylanhydrouridine (**2***b*) m.p. 218–220 °C (mixed melting point 218–220 °C). Thin-layer R_f values were 0.55 (tetrahydrofuran) and 0.70 (ethanol). Spectral properties were identical to those of the sample prepared above.

(b) **3***b* (51 mg, 0.1 mmole) and sodium bicarbonate (3 mg) were heated in dimethyl formamide (0.05 ml) at 150 °C for 30 min. The reaction mixture was worked up as in *a* to yield 40 mg of **2***b* (85%) m.p. 219–220 °C.

(c) Reaction *b* was repeated except that sodium carbonate (2 mg) was used in place of sodium bicarbonate. A yield of 38 mg (81%) of **2***b* was obtained, m.p. 218–220 °C.

(d) Reaction *c* was repeated except that **3***a* (30 mg) was used in place of **3***b* and a yield of 18 mg (72%) of **2***a* was obtained, m.p. 245–247 °C, mixed melting point 246–248 °C; Spectral properties were identical to those of the sample prepared above.

(e) **3***b* (51 mg) was dissolved in dimethyl formamide (0.05 ml) and after 30 min heating at 150 °C the products were separated by thick-layer chromatography using ethyl acetate. Two compounds appeared (R_f 0.42 and 0.84) and these were eluted to yield 5′-*O*-trityluridine 2′,3′-carbonate 25 mg, 48%; R_f 0.84 (ethyl acetate) and R_f 0.25 (ether (1); m.p. 133–135 °C; infrared spectrum (KBr disk) showed major bands at 5.57, 6.0, and 14.2 μ) and uridine 2′,3′-carbonate (10 mg, 37%; m.p. 122–126 °C; thin-layer R_f values of 0.42 (ethyl acetate) and 0.00 (ether); the infrared spectrum (KBr disk) showed prominent peaks at 5.56 and 5.95 μ).

(f) Reaction *e* was repeated except that phenol (3 mg) was added and heating was continued for 3 h. After 30 min thin-layer chromatography in ethyl acetate showed two separate spots of nearly equal intensity at R_f 0.79 (**3***b*) and 0.38 (**3***a*). After 3 h the reaction was worked up by thick-layer chromatography to yield 25 mg (92%) of uridine 2′,3′-carbonate (**3***a*), m.p. 120–125 °C.

3′,5′-Di-O-trityl-2,2′-anhydro-1-β-D-arabinofuranosyluracil (2c)

3′,5′-Di-*O*-trityluridine (40 mg, 0.055 mmole) and diphenyl carbonate (19 mg, 0.086 mmole) were heated with sodium bicarbonate (2 mg) in dimethyl formamide (0.05 ml) at 150 °C for 30 min. On cooling to room

temperature ether (2 ml) was added and the solution was applied to two thick layers plates which were developed in ethyl acetate. A band appeared at R_f 0.35 and was eluted to yield 27 mg (67%) of **2***c*, m.p. 141–143 °C; in 95% ethanol the compound showed two shoulders at 249 mμ (ε 6740) and 223 mμ; the infrared spectrum (KBr disk) displayed prominent peaks at 6.06, 6.82, and 14.3 μ.

Anal. Calcd. for $C_{47}H_{32}N_2O_6$: C, 77.35; H, 5.25; N, 3.84; Found: C, 77.33; H, 5.12; N, 3.99.

2′,5′-Di-O-trityl-3′-O-phenoxycarbonyluridine

2′,5′-Di-*O*-trityluridine (200 mg, 0.27 mmole) was heated with diphenyl carbonate (95 mg, 0.43 mmole) and sodium bicarbonate (10 mg) in dimethyl formamide (0.25 ml) at 150 °C for 30 min. The solution was cooled to room temperature, diluted with ether, and separated from a small amount of insoluble material. On addition of hexane a precipitate formed which was collected by filtration and recrystallized from ether–hexane to yield 175 mg (77%) of 2′,5′-di-*O*-trityl-3′-*O*-phenoxycarbonyluridine as a white solid, m.p. 156–159 °C. The infrared spectrum (KBr disk) displayed major peaks at 5.63, 5.85, and 14.2 μ.

Anal. Calcd. for $C_{54}H_{44}N_2O_8$: C, 76.40; H, 5.22; N, 3.30. Found: C, 76.41; H, 5.31; N, 3.20.

Acknowledgments

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Photolysis of a diterpene nitrosamine

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Photolysis of the diterpene nitrosamine, 4-*N*-nitroso-4-*N*-methyl-12-methoxy-16-norpodocarpa-8,11,-13-trien-4-amine in cyclohexane solvent gave the corresponding amine as the major product.

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The photolysis of nitrites has now become an established method, in the steroid field, for the functionalization of suitably placed saturated carbon atoms (1). In recent years work has been carried out to investigate the products resulting from the photolytic decomposition of the spectroscopically similar nitrosamines (2). In Chow's latest work (3) he has further established that simple acyclic and alicyclic *N*-nitrosodialkylamines undergo photolysis in the presence of acid to give amidoximes and the parent secondary amine.

In this present paper we have further investigated the scope of the latter reaction by studying the photolysis of the polycyclic nitrosamine, 4-*N*-nitroso-4-*N*-methyl-12-methoxy-16-norpodocarpa-8,11,13-trien-4-amine (**8**). The stereochemistry of podocarpic acid **1** is such that the axial carboxyl group at C-4 is *cis* to the C_{10}-angular methyl, the latter being forced close to the former by the steric compression offered by ring C. In this system, a nitrosamine group at C-4 might thus be expected to oxygenate the methyl at C-10.

Treatment of the acid chloride of 12-methoxypodocarpa-8,11,13-trien-16-oic acid **2** (4) with sodium azide gave the isocyanate **4** which on reduction with excess lithium aluminium hydride

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