Note

Attempted preparation of nucleoside and deoxynucleoside 3′,5′-cyclic carbonates

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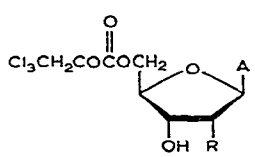
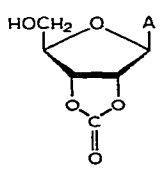
Recently, methods for the preparation of di(nucleoside) carbonates have been described[1,2]. Because of the widespread interest in purine nucleoside 3′,5′-cyclic monophosphates, it was decided to extend the "active ester" procedure[1] to the preparation of nucleoside 3,′5′-cyclic carbonates. Adenosine 3′,5′-cyclic monophosphate is generally acknowledged to be involved intracellularly in the transmission of messages signalled at the outer surfaces of cell membranes by a variety of hormones. For this reason, our initial attempts centred upon the preparation of adenosine 3′,5′-cyclic carbonate.

5′-*O*-(2,2,2-Trichloroethoxycarbonyl)adenosine (**1a**) was prepared from the 2′,3′-*O*-isopropylidene derivative[1] by treatment with 66% aqueous formic acid at room temperature. Treatment of **1a**, under "high dilution" conditions, either with sodium hydride and *N*,*N*-dimethylformamide or with potassium *tert*-butoxide and methyl sulphoxide gave adenosine 2′,3′-cyclic carbonate (**2**). This unexpected product was possibly derived *via* a di(nucleoside) carbonate, either linked 2′–5′ or 3′–5′, followed by intramolecular elimination[1] to give the stable *cis*-(cyclic carbonate) **2**. A similar mechanism could have been in operation during the direct acylation of uridine with *p*-nitrophenyl chloroformate[3]; in this case, only uridine 2′,3′-cyclic carbonate was formed and no 5′-*O*-*p*-nitrophenylcarbonic ester was observed.



1a R = OH
1b R = H

A = Adenin-9-yl



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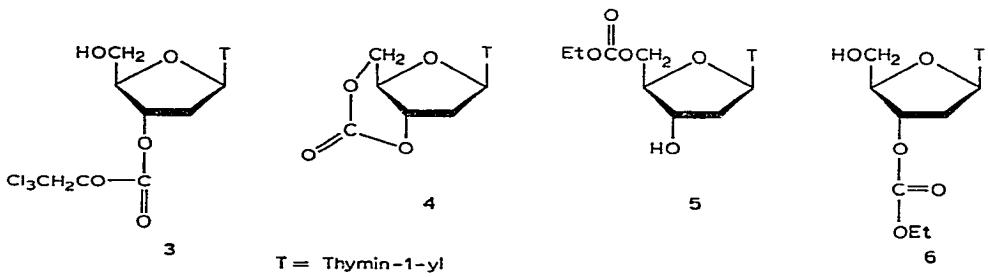
When a similar cyclisation was attempted with 2′-deoxy-5′-*O*-(2,2,2-trichloroethoxycarbonyl)adenosine (**1b**), in which the formation of a 2′,3′-*cis*-(cyclic carbonate) was excluded, only starting material, some 2′-deoxyadenosine, and a small amount of

polymeric material were observed. However, under similar cyclisation conditions, 3′-*O*-(2,2,2-trichloroethoxycarbonyl)thymidine (**3**) gave a new product with λ_{max} 267 nm and an n.m.r. spectrum in accord with that expected for thymidine 3′,5′-cyclic carbonate (**4**). In particular, the signals for the 3′ and 5′ protons were observed at δ 5.18 and 4.26, respectively; *cf.* δ 4.20 and 3.53 for thymidine. The product **4** was unstable in solution, and upon treatment with ethanol could readily be converted into two new thymidine derivatives in the ratio *ca* 1:1. These were conclusively identified as 5′-*O*-ethoxycarbonylthymidine (**5**) and 3′-*O*-ethoxycarbonylthymidine (**6**) by comparison with authentic samples prepared from thymidine.



It is concluded that, for thymidine, the highly strained and unstable 3′,5′-cyclic carbonate can be produced *via* cyclisation of the 3′-active ester but that, under similar conditions, no evidence for the formation of purine nucleoside 3′,5′-cyclic carbonates, *via* cyclisation of the 5′-active esters, could be obtained.

EXPERIMENTAL

General. — Melting points (uncorrected) were determined with a Tottoli apparatus (Buchi). N.m.r. spectra for solutions in methyl sulphoxide-d_6 were recorded with a Varian HA-100D spectrometer with Me_4Si as internal reference. Ascending thin-layer chromatograms were run on Kieselgel G_F with chloroform–ethanol in the following proportions: *A*, 1:1; *B*, 4:1; *C*, 9:1; *D*, 19:1. Kieselgel (Merck, 0.05–0.2 mm, Art. 7734) was used for column chromatography on silica gel. Samples for u.v.-spectral measurements were dissolved in ethanol.

5′-O-(2,2,2-Trichloroethoxycarbonyl)adenosine (**1a**). — 2′,3′-*O*-Isopropylidene-5′-*O*-(2,2,2-trichloroethoxycarbonyl)adenosine[1] (3.5 g) was treated with 66% aqueous formic acid (50 ml) at room temperature for 5 h. The formic acid was removed by evaporation and the residual gum dried *in vacuo* over sodium hydroxide to yield **1a** as a froth (3 g, 93%); λ_{max} 261 nm (ε 14.1×10^3); n.m.r. data: δ 8.29 (*s*, 1, H-8), 8.15 (*s*, 1, H-2), 7.26 (*s*, 2, NH_2), 5.96 (*d*, 1, H-1′), 4.90 p.p.m. (*s*, 2, CH_2).

Anal. Calc. for $C_{13}H_{14}Cl_3N_5O_6$: C, 35.3; H, 3.2; Cl, 24.0; N, 15.8. Found: C, 35.5; H, 3.3; Cl, 23.6; N, 16.0.

Adenosine 2′,3′-cyclic carbonate (**2**). — A solution of compound **1a** (220 mg) in dry methyl sulphoxide (400 ml) was treated with a freshly prepared solution of M

potassium *tert*-butoxide (0.5 ml) for 24 h at room temperature. The mixture was neutralised with Dowex-50W x8 resin (pyridinium form) and the neutral solution evaporated to a gum which was fractionated by preparative t.l.c. in solvent *A*. The major band had R_F 0.62 and the minor band, which corresponded to adenosine, had R_F 0.48. Elution of the major product with ethanol gave **2** as a white, amorphous powder (93 mg), m.p. 217–218° (dec.); lit.[4] m.p. 218–220° (dec.); λ_{max} 260 nm (ε 14.4×10^3); n.m.r. data: δ 8.27 (*s*, 1, H-8), 8.12 (*s*, 1, H-2), 7.30 (*s*, 2, NH_2), 6.22 (*d*, 1, *J* 3.0 Hz, H-1'), 5.96 (*d* of *d*, 1, *J* 8.0 and 3.0 Hz, H-2'), 5.44 p.p.m. (*d* of *d*, 1, *J* 8.0 and 3.0 Hz, H-3').

2'-Deoxy-5'-O-(2,2,2-trichloroethoxycarbonyl)adenosine (**1b**). — 2'-Deoxyadenosine (1 g) was dissolved in dry pyridine (35 ml). 2,2,2-Trichloroethoxycarbonyl chloride (0.6 ml) was added and the mixture stirred at room temperature for 72 h. The pyridine was evaporated off (30°/12 mmHg), and the residue was dissolved in chloroform and applied to a column of silica gel (100 g) which was eluted with solvent *B*. The major product **1b**, which emerged between 750–1000 ml, was isolated as a froth (570 mg, 30%); λ_{max} 261 nm (ε 13.9×10^3); n.m.r. data: δ 8.26 (*s*, 1, H-8), 8.04 (*s*, 1, H-2), 6.53 (*s*, 2, NH_2), 6.46 (*t*, 1, *J* 6.0 Hz, H-1'), 4.73 (*s*, 2, CH_2), 3.64 p.p.m. (*d*, 2, *J* 4.0 Hz, H-5').

Anal. Calc. for $C_{13}H_{14}Cl_3N_5O_5$: C, 36.6. H, 3.3; N, 16.4. Found: C, 36.3; H, 3.1; N, 16.7.

3'-O-(2,2,2-Trichloroethoxycarbonyl)thymidine (**3**). — 3'-*O*-(2,2,2-Trichloroethoxycarbonyl)-5'-*O*-tritylthymidine[1] (2 g) was dissolved in 80% aqueous acetic acid (5 ml), maintained at 100° for 15 min, and then left to cool. Water (1 ml) was added and the white precipitate of trityl alcohol removed by filtration. The filtrate was evaporated several times to dryness from water until no acetic acid remained. The residue was dissolved in chloroform and fractionated on a column of silica gel (200 g) in solvent *D*. The major product was obtained as a froth (1.1 g, 86%) which crystallised from ethanol to give **3** as white needles, m.p. 160–161°; λ_{max} 267 nm (ε 9.6×10^3); n.m.r. data: δ 7.68 (*s*, 1, H-6), 6.15 (*t*, 1, H-1'), 5.20 (*m*, 1, H-3'), 4.90 (*s*, 2, CH_2), 4.08 (*m*, 1, H-4'), 3.62 (*m*, 2, H-5'), 2.37 p.p.m. (*m*, 2, H-2').

Anal. Calc. for $C_{13}H_{15}Cl_3N_2O_7$: C, 37.4; H, 3.7; N, 6.7. Found: C, 37.3; H, 3.8, N, 6.6.

Cyclisation of **3**. — To a solution of **3** (209 mg) in anhydrous *N,N*-dimethylformamide (100 ml) was added sodium hydride (12 mg). After 1 h at room temperature, the solution was neutralised with Dowex-50W x8 (H^+) resin and evaporated to dryness to give a brown gum which was fractionated by preparative t.l.c. (solvent *B*). The major product (R_F 0.55) was eluted at 4° with ethanol. The solvent was evaporated (20°/12 mmHg) to give a white solid (60 mg); λ_{max} 267 nm; n.m.r. data: δ 7.46 (*s*, 1, H-6), 6.16 (*t*, 1, H-1'), 5.18 (*m*, 1, H-3'), 4.26 (*m*, 2, H-5'), 1.76 p.p.m. (*s*, 3, 5-CH_3). A solution of the product in methyl sulphoxide or water (pH 5.5) decomposed at room temperature to give thymidine (R_F 0.51, solvent *C*) as the major compound.

Treatment of the product with ethanol containing a trace of acid at room temperature rapidly gave **5** and **6** (R_F 0.68 and 0.74) isolated by preparative t.l.c.

(solvent *C*), and identified by n.m.r. comparison with the authentic compounds described below.

5'-O-Ethoxycarbonylthymidine (**5**). — Thymidine (1 g) was dissolved in dry pyridine (10 ml) and ethoxycarbonyl chloride (1 ml) added. The mixture was set aside for 48 h, and water (1 ml) was then added. The solution was evaporated to a gum which was crystallised from ethanol to give **5** (310 mg), m.p. 156–157°; λ_{max} 267 nm (ε 9.2×10^3); n.m.r. data: δ 7.46 (*s*, 1, H-6), 6.11 (*t*, 1, H-1'), 5.42 (*m*, 1, OH-3'), 4.28 (*m*, 3, H-3' and H-5'), 4.10 (*q*, 2, CH_2), 3.95 (*m*, 1, H-4'), 2.15 (*m*, 2, H-2'), 1.80 (*s*, 3, 5-CH_3), 1.22 p.p.m. (*t*, 3, CH_3).

Anal. Calc. for $C_{13}H_{18}N_2O_7$: C, 49.6; H, 5.8; N, 9.0. Found: C, 49.5; H, 5.7; N, 9.1.

3'-O-Ethoxycarbonylthymidine (**6**). — 3'-*O*-Ethoxycarbonyl-5'-*O*-trityl-thymidine[1] (500 mg) was dissolved in 80% aqueous acetic acid (5 ml) and maintained at 100° for 30 min. The solution was cooled, water (1 ml) was added, the precipitate of trityl alcohol was filtered off, and the acetic acid was removed by co-evaporation with water. The residue was crystallised from ethanol to give **6** (120 mg), m.p. 200–201°, λ_{max} 267 nm (ε 9.8×10^3); n.m.r. data: δ 7.71 (*s*, 1, H-6), 6.15 (*t*, 1, H-1'), 5.15 (*m*, 1, H-3'), 4.10 (*q*, 2, CH_2), 4.04 (*m*, 1, H-4'), 3.62 (*m*, 2, H-5'), 2.30 (*m*, 2, H-2'), 1.78 (*s*, 3, 5-CH_3), 1.22 p.p.m. (*t*, 3, CH_3).

Anal. Calc. for $C_{13}H_{18}N_2O_7$: C, 49.6; H, 5.8; N, 9.0. Found: C, 50.0; H, 5.9; N, 9.1.

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