A Novel One-step Procedure for the Conversion of Thymidine into 2,3′-Anhydrothymidine

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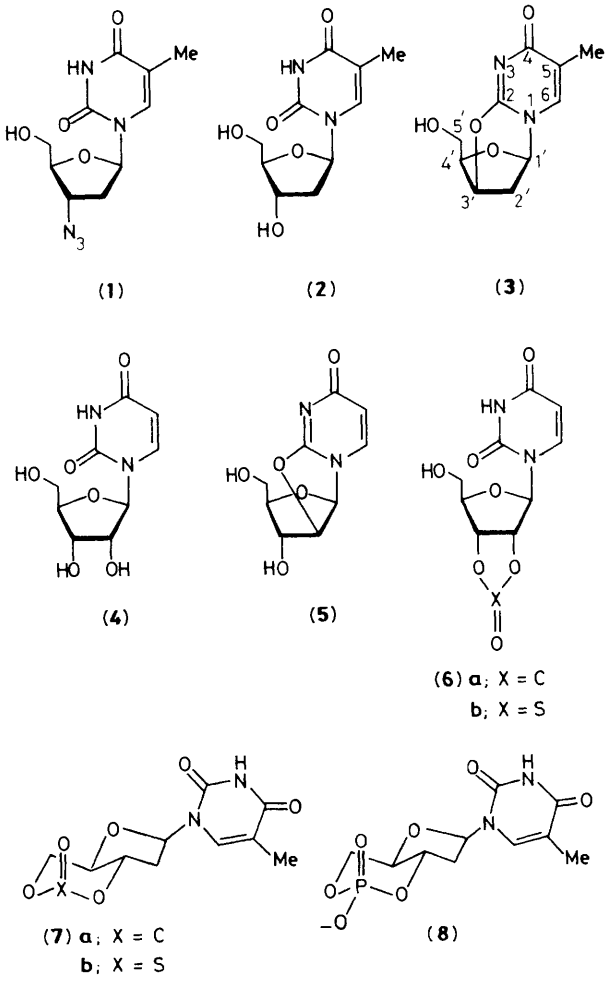
2,3′-Anhydrothymidine (**3**) is obtained in *ca.* 65% yield by heating thymidine (**2**) with an excess of diphenyl sulphite in dimethylacetamide solution; (**3**) reacts with lithium azide to give 3′-azido-3′-deoxythymidine [AZT, (**1**)] in good yield.

A number of 2′,3′-dideoxynucleoside derivatives have so far proved to be potent and selective inhibitors of HIV-1 replication.[1] Currently, the most important of these derivatives is 3′-azido-3′-deoxythymidine [ATZ, (**1**)] which has been licenced in several countries for the treatment of AIDS patients. In connection with a research programme directed towards the synthesis of 2′,3′-dideoxynucleoside derivatives, we have sought a convenient procedure for the conversion of thymidine (**2**) into 2,3′-anhydrothymidine (**3**).

When uridine (**4**) is heated with diphenyl carbonate[2] at 150 °C in hexamethylphosphoric triamide[3] solution, in the presence of a catalytic quantity of sodium hydrogen carbonate, 2,2′-anhydrouridine (**5**) is obtained in nearly quantitative yield. It may reasonably be assumed[2] that uridine 2′,3′-cyclic carbonate (**6a**) is an intermediate in this reaction. However, we have found that when thymidine (**2**) is allowed to react with diphenyl carbonate under the same conditions, no 2,3′-anhydrothymidine (**3**) can be detected in the products. This is perhaps not surprising as the putative intermediate 3′,5′-cyclic carbonate (**7a**) would be expected to be strained.

A possible way around this difficulty was suggested by the report[4] that 2,2′-anhydrouridine (**5**) is obtained in satisfactory yield when uridine 2′,3′-cyclic sulphite (**6b**) is heated at 80 °C, in the presence of sodium acetate in dimethylformamide solution. We now report that when uridine (**4**) is heated with a slight excess of diphenyl sulphite[5] at 150 °C in hexamethylphosphoric triamide solution, in the presence of a catalytic quantity of sodium hydrogen carbonate, 2,2′-anhydrouridine (**5**) is obtained in good yield. Furthermore, when thymidine (**2**) is heated with a four-fold excess of diphenyl sulphite at 156 °C in dimethylacetamide solution in the presence of a catalytic quantity of 1-methylimidazole and the products are then subjected to a mildly alkaline hydrolytic work-up, 2,3′-anhydrothymidine (**3**) is obtained† as a virtually pure colourless solid in almost 65% yield. It is reasonable to assume that this reaction proceeds *via* an intermediate cyclic sulphite (**7b**) which would not be expected to be especially more strained than the corresponding readily accessible 3′,5′-cyclic phosphate (**8**).[6]

It seems likely that diphenyl sulphite and related sulphite esters will prove to be generally effective reagents for the conversion of pyrimidine 2′-deoxynucleosides into their 2,3′-anhydro derivatives. Kowollik *et al.*[7] have previously reported that when thymidine (**2**) is heated with 2 molar equiv. of 2-chloro-1-diethylamino-1,1,2-trifluoroethane[8] in acetone or dimethylformamide solution at 70 °C for 30 min, 2,3′-anhydrothymidine (**3**) is obtained in 75% yield. However, Glinski *et al.*[9] subsequently repeated this reaction, starting with a relatively large quantity (*ca.* 0.2 mol) of thymidine (**2**) and obtained (**3**) only in 40% yield. Diphenyl sulphite[5] is more accessible than 2-chloro-1-diethylamino-1,1,2-trifluoro-



† The following procedure is recommended for the preparation of 2,3′-anhydrothymidine (**3**). A flask containing a stirred mixture of thymidine (5.0 g, 20.6 mmol), diphenyl sulphite (19.34 g, 82.6 mmol), 1-methylimidazole (0.34 ml, 4.27 mmol), and *N*,*N*-dimethylacetamide (50 ml) was immersed in an oil bath, maintained at 156 ± 1 °C. After 45 min, the products were cooled to 0 °C and then poured, with stirring, into a cooled (to 0 °C) mixture of triethylamine (50 ml) and water (90 ml). After 40 min, by which time the mixture had warmed up almost to room temperature, the resulting solution was extracted with chloroform (4 × 50 ml). The remaining aqueous layer was concentrated under reduced pressure and the viscous oil obtained was dissolved in absolute ethanol (30 ml), and the solution was re-evaporated. After one further evaporation from absolute ethanol solution (30 ml), the residue was triturated with ether (3 × 30 ml). Dichloromethane (50 ml) was then added and the resulting colourless precipitate was collected by filtration and washed with dichloromethane (2 × 10 ml). After the combined filtrate and washings had been concentrated to *ca.* 30 ml, light petroleum (b.p. 30—40 °C; 15 ml) was added, and the resulting mixture was refrigerated (4 °C) for 24 h. A second crop of colourless solid was obtained; this was collected by filtration and was washed with dichloromethane (2 × 5 ml). The two crops of colourless solid were combined and dried *in vacuo* at 75 °C to give virtually pure 2,3′-anhydrothymidine (3.0 g, 64.8%), identical to authentic material.[10]

ethane[8] and it would therefore seem that the present cyclization procedure is to be preferred to that of Kowollik *et al.*[7] The first published synthesis[10] of (**3**) involved five steps.

Unprotected 2,3′-anhydronucleosides, such as (**3**), are useful intermediates in the synthesis of 2′,3′-dideoxynucleoside derivatives. Thus we have found that when 2,3′-anhydrothymidine (**3**) is heated with 2 molar equiv. of lithium azide in dimethylacetamide solution at 123 °C for 3 h, ATZ (**1**) is obtained and may be isolated from the products in 71% yield. The present ATZ synthesis proceeds in *ca.* 46% overall yield for the two steps starting from thymidine (**2**), and compares very favourably with other syntheses previously reported[9,11] in the literature.

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