Ribonucleoside 2′,3′-Orthocarbonates

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Summary Ribonucleosides undergo acid-catalysed exchange with tetramethyl orthocarbonate to give 2′,3′-*O*-dimethoxymethylidene derivatives.

RIBONUCLEOSIDES (I) react readily with tetramethyl orthocarbonate[1] in anhydrous dioxan solution, in the presence of toluene-*p*-sulphonic acid, to give the corresponding 2′,3′-*O*-dimethoxymethylidene derivatives (II) in satisfactory yields (see Table). This reaction corresponds to the previously reported[2] acid-catalysed orthoester exchange between ribonucleosides and trimethyl orthoesters of formic, acetic, and benzoic acids.

Reaction between adenosine and tetramethyl orthocarbonate,† in the presence of a slight excess of acid, gave 2′,3′-*O*-dimethoxymethylideneadenosine (II; B = III) which was isolated as a colourless crystalline solid.‡ Uridine required much less acid to catalyse the exchange reaction, but the product (II; B = IV) was not obtained crystalline. Although cytidine did not undergo orthoester exchange under the conditions examined, N^4-acetylcytidine was converted into its 2′,3′-*O*-dimethoxymethylidene derivative (II; B = Vb) in good yield. Treatment of the latter compound with methanolic ammonia gave 2′,3′-*O*-dimethoxymethylidenecytidine.

2′,3′-O-Dimethoxymethylidene derivatives of ribonucleosides

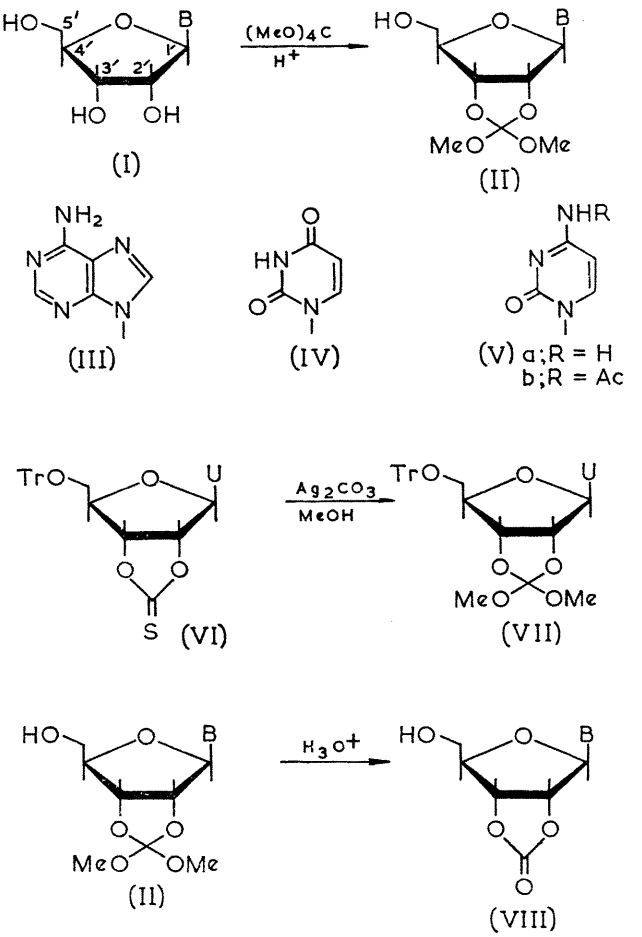
Ribonucleoside	2′,3′-*O*-Dimethoxymethylidene derivative Yield (%)[a]	m.p.
Adenosine (I; B=III)	52	178—180°
Uridine (I; B = IV)	42	
N^4-Acetylcytidine (I; B = Vb)	58	159—160°
Cytidine (I; B = Va)	82	136—137°

[a] Based on nucleoside as starting material, except in the case of the cytidine derivative (II; B = Va) where the yield is based on N^4-acetyl-2′,3′-*O*-dimethoxymethylidenecytidine (II; B = Vb) as starting material.

One example of a 2′,3′-*O*-dimethoxymethylidene ribonucleoside derivative has previously been described. Ruyle *et al.*[3] treated a methanolic solution of 5′-*O*-trityluridine 2′,3′-thionocarbonate (VI) with silver carbonate and obtained a product, m.p. 198—200°, which they formulated as (VII). We have prepared (VII) from 5′-*O*-trityluridine by the orthoester exchange reaction and, apart from its lower m.p. (183—185°), our product appears to be identical to that described by Ruyle *et al.*[3]

2′,3′-*O*-Dimethyoxymethylidene ribonucleoside derivatives (II) have several characteristic properties. Firstly, their methoxy-protons resonate as two sharp singlets, with a chemical shift difference of *ca.* 0·1 p.p.m., in the region of τ 6·6; secondly, they are unaffected by treatment with alkali; and thirdly, they are quantitatively converted into the corresponding 2′,3′-carbonate esters (VIII) by treatment with aqueous acid under mild conditions. Thus the hydrolysis of 2′,3′-*O*-dimethoxymethylideneadenosine (II; B = III) to adenosine-2′,3′-carbonate (VIII; B = III), in 0·01N-hydrochloric acid at 20°, displayed first-order kinetics with $t_{\frac{1}{2}}$ = 10 min.

For preparative purposes, it was more convenient to carry out the hydrolysis in 98% formic acid solution. In this way, the 2′,3′-carbonates of adenosine,[4] uridine,[5] and N^4-acetylcytidine (VIII; B = III, IV, and Vb, respectively) were prepared in high yields from the corresponding dimethoxymethylidene derivatives. N^4-Acetylcytidine 2′,3′-carbonate (VIII; B = Vb), was also prepared by the action of diphenyl carbonate[4] on N^4-acetylcytidine in dimethylformamide solution.



Tr = Ph_3C; U = uracil-1 (IV).

2′,3′-*O*-Dimethoxymethylidene ribonucleoside derivatives (II) are likely to find use as synthetic intermediates. In the first place, they constitute a novel type of 2′,3′-protected ribonucleoside with a base-stable blocking group which is transformed, under aqueous acidic conditions, into a base-labile (acid-stable) blocking group. Secondly, their availability leads to a convenient general synthesis of ribonucleoside 2′,3′-cyclic carbonates.[4,5]

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† A two-fold excess of orthoester was generally found to be sufficient.
‡ Satisfactory analytical data have been obtained for all new compounds described.

[1] Prepared by the procedure described for tetraethyl orthocarbonate; see J. D. Roberts and R. E. McMahon, *Organic Synth.*, 1952, **32**, 68
[2] M. Jarman and C. B. Reese, *Chem. and Ind.*, 1964, 1493; C. B. Reese and J. E. Sulston, *Proc. Chem. Soc.*, 1964, 214; B. E. Griffin, M. Jarman, C. B. Reese, and J. E. Sulston, *Tetrahedron*, 1967, **23**, 2301; H. P. M. Fromageot, B. E. Griffin, C. B. Reese, and J. E. Sulston, *ibid.*, 1967, **23**, 2315.
[3] W. V. Ruyle, T. Y. Shen, and A. A. Patchett, *J. Org. Chem.*, 1965, **30**, 4353.
[4] A. Hampton and A. W. Nichol, *Biochemistry*, 1966, **5**, 2076.
[5] R. L. Letsinger and K. K. Ogilvie, *J. Org. Chem.*, 1967, **32**, 296.