Novel Procedure for Regioselective 2′-*O*-Deacylation of Fully Acylated Purine and Pyrimidine Ribonucleosides with Hydrazine Hydrate[1]

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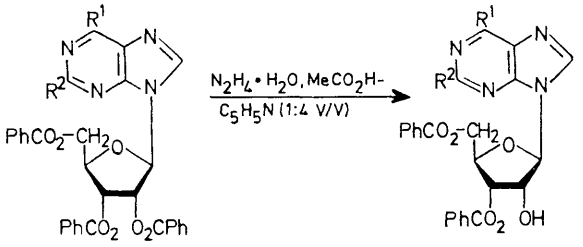
Summary Hydrazinolysis of N^6,N^6,2′,3′,5′-pentabenzoyladenosine, N^2,2′,3′,5′-tetrabenzoylguanosine, and 2′,3′,5′-tri-*O*-benzoylinosine in AcOH–pyridine was regioselectively induced at the 2′-position among the three alcoholic functions to give the corresponding 2′-OH derivatives in good yields; this procedure also proved effective for the partial debenzoylation of fully benzoylated uridine and cytidine although the regioselectivity observed was not as good.

ALTHOUGH the partial protection of hydroxy-groups of ribonucleosides has been attempted by acetylation,[2] tosylation,[3] benzylation,[4] silylation,[5] tritylation,[6] 3-benzoylpropionylation,[7] partial hydrolysis of their 2′,3′-orthoacetates,[8] and partial methanolysis which involves fully benzoylated cytidine[9] *etc.*, the expected regioselectivity has not been attained. Thus mixtures of several protected nucleosides were obtained which required chromatographic separation procedures, creating difficulties for the synthesis of ribonucleotide oligomers. Therefore, we set out to develop a new method for specific protection of nucleoside hydroxy-groups.

The unusual acidity of the 2′-OH group of uridine and cytidine, suggested by their partial 2′-*O*-benzylation,[4] and the fact that the C(2′)–O(2′) bond is the shortest among the three alcoholic groups at the 2′, 3′, and 5′ positions in a series of purine ribonucleosides (proved by *X*-ray crystal structure analysis[10]), prompted us to investigate a potentially specific 2′-*O*-deacylation of fully acylated purine and pyrimidine ribonucleosides. The specific *N*-debenzoylation



(1) R^1 = N(PhCO)$_2$, R^2 = H
(2) R^1 = NH_2, R^2 = H
(3) R^1 = OH, R^2 = NHCOPh
(4) R^1 = OH, R^2 = NHCOPh
(5) R^1 = OH, R^2 = H
(6) R^1 = OH, R^2 = H

of 2′-deoxyadenosine and -cytidine benzoates with hydrazine hydrate[11] was used for this purpose since hydrazinolysis has commonly been used for the preparation of hydrazides from alkyl esters of the corresponding carboxylic acids.[12]

Treatment of N^6,N^6,2′,3′,5′-pentabenzoyladenosine (**1**) (2 mmol) with hydrazine hydrate (4—8 mmol) in AcOH–pyridine (1 : 4) at room temperature for 7 days or at 80—85

°C for 12 h, followed by quenching with acetone, evaporation, separation on a silica gel column (MeOH–$CHCl_3$ as eluant), and crystallization of the product (80% yield),† gave 3′,5′-di-*O*-benzoyladenosine (**2**) [m.p. 193—194 °C (from $CHCl_3$)] (70% yield).‡ Similar treatment of N^2,2′,3′,5′-tetrabenzoylguanosine (**3**) and 2′,3′,5′-tri-*O*-benzoylinosine (**5**) gave N^2,3′,5′-tribenzoylguanosine (**4**) [m.p. 229—230 °C (from MeOH)] (crude, 70%; pure, 48% yield) and 3′,5′-di-*O*-benzoylinosine (**6**) [m.p. 163·5—164·5 °C (from MeOH)] (crude, 68%; pure, 52% yield).†‡§ However, 2′,3′,5′-tri-*O*-benzoyluridine was found to give a 2:1 mixture of 3′,5′- and 2′,5′- di-*O*-benzoyluridine in 65% yield,‡¶ and treatment of N^4,2′,3′,5′-tetrabenzoylcytidine gave a mixture of the di-*O*-benzoates in 21% yield.‡**

In spite of the low regioselectivity in the hydrazinolysis of uridine and cytidine acylates, this novel procedure is more regioselective for 2′-*O*-acyl groups, and is far more advantageous than the procedure involving partial hydrolysis of 2′,3′-orthoacetates which until now has been generally accepted as the most effective method.[2–9]

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† The ^{1}H n.m.r. spectra of the isolated products showed that they contained the corresponding 3′-OH isomers (< 10%).

‡ Satisfactory elemental analyses, and u.v., and ^{1}H n.m.r. spectral data were obtained,

§ The same trend was observed in the hydrazinolysis of the corresponding acetates, *e.g.*, 3′,5′-di-*O*-acetyladenosine [m.p. 151—152 °C (from MeOH)] was isolated in 60% yield.

¶ The mixture was successfully separated by fractional crystallization from methanol.

** In this case, a considerable amount of by-products was formed; one of them was isolated in 27% yield and confirmed as being 4-isopropylidenehydrazino-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrimidin-2(1*H*)-one.

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