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METHOXYACETYL AS A PROTECTING GROUP IN RIBONUCLEOSIDE CHEMISTRY

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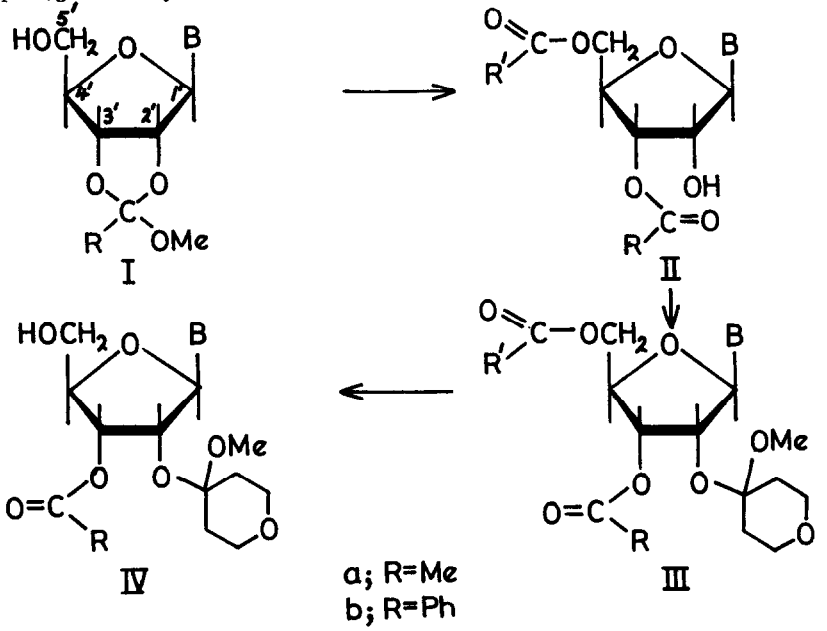
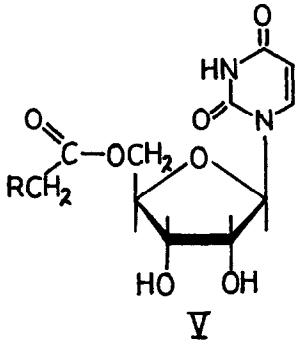
Ribonucleoside derivatives with acid-labile 2'- and base-labile 3'-protecting groups are required as intermediates in our approach to oligoribonucleotide synthesis (1). The immediate precursors (III) of these derivatives must be so designed that their 5'-O-acyl functions may be removed by basic hydrolysis under relatively mild conditions, thereby ensuring that their 3'-ester groups (generally acetates of benzoates) remain intact.



We found that 3'-O-benzoyl-5'-O-formyluridine (IIb; R' = H, B = uracil) (2) reacted smoothly with 4-methoxy-5,6-dihydro-2H-pyran (3) in the presence of toluene-p-sulphonic acid to give the corresponding ketal (IIIb; R' = H, B = uracil) which, on treatment with dilute methanolic ammonia, gave the required derivative (IVb; B = uracil) (4). The latter was isolated as a pure crystalline compound (5), m.p. 207-208°, in 62% yield. Although this suggested a general

synthetic method, the comparatively high lability of the formyl group, even in neutral alcoholic solution, tended to limit the yields of the intermediate diacyl derivatives (II). It therefore seemed that an alternative protecting group was required.



V

a; R=H
b; R=MeO
c; R=PhO

Consideration of acyl groups which were most likely to be removable selectively in the presence of acetate and benzoate functions, led us to investigate the solvolytic behaviour of 5'-O-methoxy- and -phenoxy-acetyluridines (Vb and Vc, respectively) (6). The latter substrates (7) were obtained in good yields by treatment of 2',3'-O-isopropylideneuridine with methoxyacetic (8) and phenoxyacetic (9) anhydrides, respectively, followed in each case by an acidic hydrolysis step to remove the isopropylidene group.

TABLE 1

Action of Ammonia on 5'-O-Acyl-uridine Derivatives (V) at 22°

Substrate	Reagent	$t_{\frac{1}{2}}$ (min)
Va	NH_3/MeOH[a]	59
Vb	NH_3/MeOH	2.5
Vc	NH_3/MeOH	<1[b]
Va[c]	0.155N-aqueous NH_3[d]	191
Vb	0.155N-aqueous NH_3	10.4
Vc	0.155N-aqueous NH_3	3.9

[a] Prepared by diluting saturated (at 0°) methanolic ammonia with an equal volume of methanol. [b] This reaction was too fast for $t_{\frac{1}{2}}$ to be measured accurately. [c] The molarities of the substrates in the aqueous reactions were in the range 0.01-0.015. [d] The pH of this reagent was 10.77.

The solvolysis of 5'-O-acetyl-, -methoxyacetyl-, and -phenoxyacetyluridines (Va, Vb, and Vc, respectively) was investigated both in methanolic and

aqueous ammonia solutions: first-order plots were obtained, and the half-times of reaction were as indicated in table 1. It can be seen that the ratio of the solvolysis rates of the methoxyacetyl (Vb) and acetyl (Va) derivatives was ca. 20, in both methanolic and aqueous solutions. Although this ratio was greater still (ca. 50) for the phenoxyacetyl (Vc) and acetyl derivatives, it was estimated that the methoxyacetyl protecting group would be quite satisfactory for the present purposes.

TABLE 2

Preparation of 3'-O-Acyl-5'-O-Methoxyacetyl Ribonucleoside Derivatives (IIa or IIb; R' = $MeOCH_2$) and the Desired Ketal Esters (IVa or IVb)

Nucleoside	R	B	Compound II m.p.(°C)	Compound II Yield[a]	Compound IV m.p.(°C)	Compound IV Yield[b]
Uridine	Me	uracil	143-145	74%	201-203	78%
Cytidine	Me	N^4-benzoylcytosine	99-100	68%[c]	203-204	48%
Adenosine	Ph	adenine	198-199	69%	233-235	60%
Guanosine	Me	N^2-benzoylguanine	179-180	74%	214-215	67%

[a] Yields which are based on the corresponding 2',3'-O-methoxyalkylidene derivatives (I) as starting materials, represent mixtures of the 3'-acetates or benzoates (IIa or IIb) and their 2'-isomers. High recoveries of the crystalline 3'-esters (II) can be obtained from such mixtures as the isomers undergo equilibration in solution. [b] Overall yield, based on the corresponding derivative II. [c] In this case, the isomeric 2'-O-acetyl-5'-O-methoxyacetyl-N^4-benzoylcytidine was also obtained crystalline (m.p. 155-157°).

2',3'-O-Methoxyalkylidene derivatives (2) of the four common ribonucleosides (Ia or Ib) (10) were treated with methoxyacetic anhydride, and the products submitted to mild acidic hydrolysis. In each case, 3'-O-acetyl (or benzoyl)- 5'-O-methoxyacetyl ribonucleoside derivatives (IIa or IIb; R' = $MeOCH_2$) could be isolated in a pure crystalline state (11) (see table 2); these derivatives were then allowed to react with 4-methoxy-5,6-dihydro-2H-pyran (3) in dioxane solution, in the presence of mesitylene- or p-toluene-sulphonic acid, to give the intermediates (III). The latter were not isolated, but were treated with methanolic ammonia (half-saturated at 0°) for 10 min at 20° to give the desired ketal esters (IVa or IVb), which were obtained as crystalline compounds in satisfactory yields (12) (see table 2).

Insomuch as the 3',5'-diesters (II) can readily be isolated in a

pure crystalline state, and the fully protected intermediates (IIIa or IIIb; R' = $MeOCH_2$) selectively de-acylated, the methoxyacetyl function has been shown to have the desired properties as a protecting group in ribonucleoside chemistry. It seems likely that the present approach would be of general application in sugar chemistry and in related fields.

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REFERENCES

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(2) H. P. M. Fromageot, B. E. Griffin, C. B. Reese and J. E. Sulston, Tetrahedron 23, 2315 (1967).

(3) C. B. Reese, R. Saffhill and J. E. Sulston, J. Am. Chem. Soc. 89, 3366 (1967).

(4) Dr. J. E. Sulston had previously prepared 2'-O-tetrahydropyranyl-3'-O-benzoyluridine in a similar way (J. E. Sulston, Ph.D. Thesis, Cambridge University, 1966, p. 85).

(5) Satisfactory analytical data were obtained for all new compounds described.

(6) The pKa's of acetic, methoxyacetic, phenoxyacetic and formic acids are 4.76, 3.53, 3.12 and 3.77, respectively (H. C. Brown, D. H. McDaniel and O. Häblinger in "Determination of Organic Structures by Physical Methods", E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, 1955, pp. 573, 578). Although methoxy- and phenoxy-acetic acids are both stronger than formic acid, it seemed possible, on steric grounds, that their esters would undergo base-catalyzed solvolysis less readily.

(7) 5'-O-Methoxy- and -phenoxy-acetyluridines were obtained as colourless crystalline solids with m.p.'s of 134-135° and 122-123°, respectively.

(8) Eastman Kodak Co., U.S. Patent 2,017,182 (1932).

(9) M. Koller and P. De Ruggien, Boll. soc. ital. biol. sper. 31, 1154 (1955).

(10) In the cases of cytidine and guanosine, the starting materials were the N-benzoyl-2',3'-O-methoxyalkylidene derivatives of the nucleosides (see table 2).

(11) All these derivatives were orientated by n.m.r. spectroscopy (H. P. M. Fromageot, B. E. Griffin, C. B. Reese, J. E. Sulston and D. R. Trentham, Tetrahedron 22, 705 (1966)), and found to be free from the isomeric 2'-acetates or benzoates.

(12) Under these reaction conditions, the methoxyacetyl group in, for example, the uridine derivative (IIIa; R' = $MeOCH_2$, B = uracil) was removed at a rate significantly greater than 24 times (see table 1) that of the acetyl group. This was presumably due to the latter being attached to a comparatively hindered secondary hydroxyl function. Thus, a negligible amount of de-acetylation occurred in 10 min.