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2-CHLOROETHYL ORTHOFORMATE AS A REAGENT FOR PROTECTION IN NUCLEOTIDES SYNTHESIS

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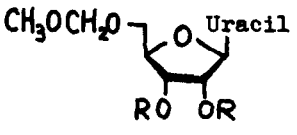
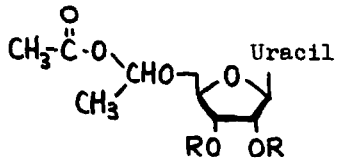
Acetal derivatives are commonly used in the chemistry of nucleosides and nucleotides as a protection of alcoholic hydroxyl (1,2,3). The acetals are very stable toward alkalies and anionoid reagents but are easily hydrolyzed by diluted mineral acid solution at room temperature. For example, treating with mineral acid, purine nucleosides, especially adenosine derivatives, degrade to adenine and ribose.

In the present experiments, the exploration of a suitable protecting group which is labile by the effect of aqueous solution, contains weakly acidic substances as acetic acid, was tried. Firstly, the stability of acetals of nucleosides has been studied on formaldehyde 2',3'-O-dibenzoyl uridine 5'-methyl acetal (I), prepared from 2',3'-O-dibenzoyl uridine and methyl chloromethyl ether, and formaldehyde 2',3'-O-dibenzoyl uridine 5'-acylal (II), prepared from 2',3'-O-dibenzoyl uridine and vinyl acetate, both of which proved to be too stable in 80% aqueous acetic acid.

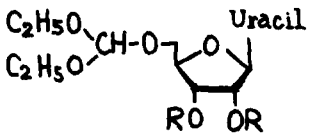


(I)



(II) R: Benzoyl

Based on these results, dialkoxymethyl group was chosen as a protecting group instead of acetals. It was found that 2',3'-O-dibenzoyl uridine diethyl orthoformate (III), prepared from 2',3'-O-dibenzoyl uridine and ethyl orthoformate, is unfortunately too labile to give hydrolyzed product, 2',3'-O-dibenzoyl uridine, even when it was dissolved in 80% aqueous acetic acid.



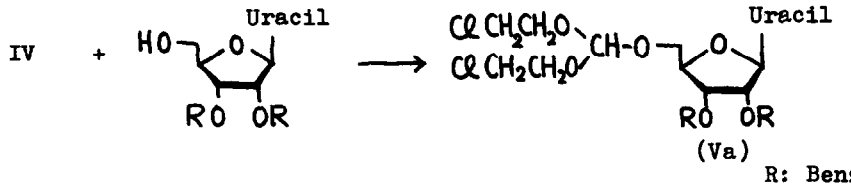
(III)

Next, 2-chloroethyl orthoformate (IV) was prepared by the reaction of methyl orthoformate and three equiv of 2-chloroethanol with the assumption that the stability of nucleosides orthoformate can be increased by introducing a chlorine atom on β-position of ethyl group. The compound, IV, was synthesized by treating methyl orthoformate with 2-chloroethanol at 100° for 2 hours and the resulting mixture was distilled to give 40% yield of IV as colorless liquid, bp. 154-156°C (11mmHg); Anal. Calcd. for $C_7H_{13}O_3Cl_3$: C,33.39; H,5.16. Found: C,33.52; H,5.44.

$$HC(OCH_3)_3 + 3\ ClCH_2CH_2OH \longrightarrow HC(OCH_2CH_2Cl)_3 + 3\ CH_3OH$$

(IV)

When 2',3'-O-dibenzoyl uridine was heated with a large excess amount of 2-chloroethyl orthoformate (IV) at 100° for 2 hours, the corresponding uridine 5'-orthoformate (Va) was obtained in 76% yield. The compound, Va, can be easily separated by silicagel thinlayer chromatography developed by a mixted solvent of chloroform and methanol (15:1 v/v).



R: Benzoyl

In similar manner, thymidine, adenosine, inosine, guanosine and ribofuranosyl theophilline, orthoformates are obtained in high yields as shown in the following Table.

TABLE

Preparation of Nucleoside Di-2-chloroethyl Orthoformates

No.	Di-2-chloroethyl Orthoformate	Yield (%)	Reaction Time(min)	Temp.(°C)
Va	2',3'-O-dibenzoyl uridine 5'-orthoformate	76	30	100
Vb	3'-O-acetyl thymidine 5'-orthoformate	80	30	100
Vc	5'-O-trityl thymidine 3'-orthoformate	80	30	100
Vd	2',3'-O-isopropylidene adenosine 5'-orthoformate	72	10	100
Ve	2',3'-O-isopropylidene inosine 5'-orthoformate	70	20	100
Vf	2',3'-O-isopropylidene guanosine 5'-orthoformate	30	20	100
Vg	2',3'-O-isopropylidene ribofuranosyl theophylline 5'-orthoformate	47	10	100

The di-2-chloroethoxymethyl group can be easily removed by 80% acetic acid at room temperature for only 1 hour but is stable in alkaline conditions.

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