THE REACTION OF 1,3-DICHLORO-1,1,3,3-TETRAISOPROPYL-DISILOXANE WITH CYTOSINE ARABINOSIDE AND 1-(6-DEOXY--α-L-TALOFURANOSYL)URACIL

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1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (*I*) reacts with cytosine arabinoside (*II*) in pyridine under the formation of 3′,5′-O-(tetraisopropyldisiloxane-1,3-diyl)cytosine arabinoside (*IIIa*) and with 1-(6′-deoxy-α-L-talofuranosyl)uracil (*V*) under the formation of 2′,3′-O-(tetraisopropyldisiloxane-1,3-diyl) 1-(6-deoxy-α-L-talofuranosyl)uracil (*VIa*).

1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (*I*) was recently developed for simultaneous protection of 3′- and 5′-hydroxyl functions in ribonucleosides[1,2]. The specific reaction of *I* in ribonucleoside series was explained on the basis of very fast reaction of *I* with the primary 5′-hydroxyl function followed by slower intramolecular ring closure with secondary 3′-hydroxyl. The 3′,5′-O-protected ribonucleosides represent key intermediates for the synthesis of natural ribointernucleotidic bond[3].

The reagent *I* was not yet tested on nucleosides with modified carbohydrate moiety. In this paper results in that direction are presented. The first modified nucleoside studied was cytosine arabinoside (*II*). Taking into account the primary reaction on 5′-hydroxyl function, a slight possibility existed for the ring closure to 2′-hydroxyl function. It was already known that N^4-benzoyl-cytosine arabinoside 5′-phosphate afforded by cyclisation exclusively 2′,5′-cyclic phosphate[4]. The reaction of *II* with equimolar amount of *I* in pyridine gave one product only.

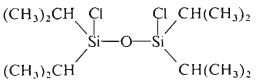
The position of 2′-hydroxyl function was established by comparison of ^{1}H-NMR spectra of the product *IIIa* and its acylated derivatives *IIIb*, *IIIc*. The signal of $H_{2'}$ in *IIIa*, forming doublet of doublets at δ 4·54, was shifted downfield by acetylation to 5·75 (*IIIb*) and by *in situ* acylation with trichloroacetyl isocyanate (TAI method[5]) to δ 5·99 (*IIIc*). Such large acylation shifts were in accordance with the known[5] magnitude of α-acylation shifts.

The cyclisation of primarily formed 5'-O-silyl derivative led to 3',5'-ring closure. The 3',5'-O-protected derivative of cytosine arabinoside *IIIa* represents a useful intermediate for further derivatisation according to methods described in ref.[1]. Further evidence of 3',5'-cyclic structure was brought by acidic cleavage of *IIIa* with 0·2M hydrochloric acid. This reaction gave, in analogy to acidic cleavage of 3',5'-O--(tetraisopropyldisiloxane-1,3-diyl) derivatives of ribonucleosides[1], the 3'-O-silyl derivative *IVa*.

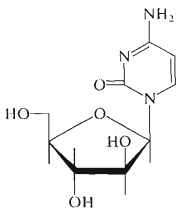
Position of the free hydroxyl function was established by comparison of ^{1}H-NMR spectra of *IVa* and its acylated derivatives *IVb*–*IVd*. In the spectrum of *IVa* the protons $H_{2'}$, $H_{3'}$, $H_{4'}$ and $H_{5'}$ formed a complex multiplet in the region of δ 3·8 to 4·5. After *in situ* acylation with trichloroacetyl isocyanate the proton signals of $H_{2'}$ appeared at δ 5·53 and $H_{3'}$ at δ 4·8 (in *IVd*). Similarly, the protons $H_{2'}$ and $H_{3'}$ formed analogous signals in spectrum of *IVb* at δ 5·44 and 4·4. These chemical shifts are consistent with the location of siloxalyl group at 3'-position. The compound *IVb* afforded after treatment with trichloroacetyl isocyanate the trichloroacetylcarbamoyl derivative *IVc* (NH δ 8·85) the spectrum of which is practically identical with that of *IVb*, except for a small downfield shift of $H_{3'}$ signal (δ 4·48) and for changes in isopropyl group signals. These findings are in accordance with structures *IVa*–*IVd*.

The primary center of the reaction of ribonucleosides is the primary 5'-hydroxyl function. Therefore it was highly interesting to test the behaviour of a modified nucleoside bearing a secondary hydroxyl group in 5'-position. Recently studied nucleosides derived from 6-deoxy-L-talose and 6-deoxy-D-allose[6–13] are examples of this type of compounds. For our study we selected 1-(6-deoxy-α-L-talofuranosyl)-uracil (*V*), recently prepared in this laboratory[14–16]. The compound *V* afforded by the action of *I* in pyridine a single product. *In situ* acylation of the product with trichloroacetyl isocyanate induced large downfield shift of the $H_{5'}$ signal from δ 4·0 (*VIa*) to δ 5·26 (*VIb*). This finding clearly indicated the structure with free 5'-hydroxy function.

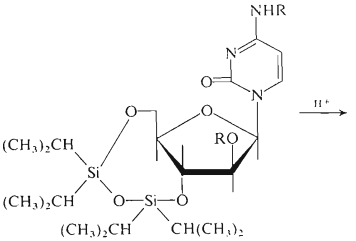
The results are interesting from the point of view of the reaction mechanism. The absence of the primary hydroxyl function of 5'-carbon completely changes the reaction course affording 2',3'-O-(tetraisopropyldisiloxane-1,3-diyl) derivative. On the other hand the substitution of this type in *ribo* series can be achieved with 5'-O-protected nucleosides only[1,2]. If the steric hindrance would be the only determining factor, the formation of 3',5'-O-, along with 2',3'-O-derivative could be expected. The formation of 2',3'-O-(tetraisopropyldisiloxane-1,3-diyl) derivative might be explained by the fact that the *cis*-diol grouping possess higher acidity compared to secondary hydroxy function on $C_{(5')}$. The exclusive formation of the 3',5'-cyclic derivative of cytosine arabinoside (*IIIa*) and of the 2',3'-cyclic derivative of 1-(6-deoxy-α-L-talofuranosyl)uracil (*VIa*) might be also explained by the influence of conformational factors affecting the pseudorotation about the $C_{(4')}-C_{(5')}$ bond. This possible role can be illustrated in the case of the compound *VI* on the staggered conformers *A*, *B*



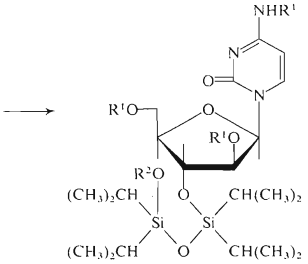
I



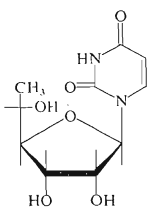
II



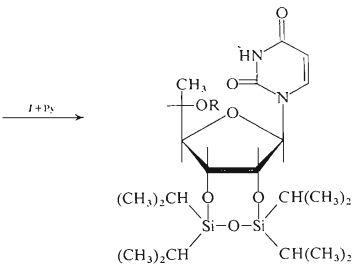
IIIa, R = H
IIIb, R = $COCH_3$
IIIc, R = $CONHCOCCl_3$



IVa, R^1 = H, R^2 = OH
IVb, R^1 = $COCH_3$, R^2 = OH
IVc, R^1 = $COCH_3$, R^2 = $CONHCOCCl_3$
IVd, R^1 = R^2 = $CONHCOCCl_3$

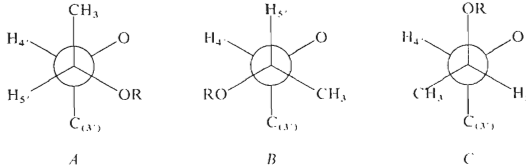


V



VIa, R = H
VIb, R = $CONHCOCCl_3$

and *C*. It was already shown by ^{1}H-NMR spectra that the *talo* and *allo* furanosides exhibited hindered rotations on the $C_{(4')}-C_{(5')}$ bond with the dominant population of one of the rotamers. The preferred position of a bulky substituent at $C_{(5')}$ (OR group) is that of the rotamer *B*. In the case of free OH group the possible rotamers *A* and *C* could be assumed. Preferential orientation of 5-'OH group corresponding



A *B* *C*

to *A* and *C* would also prevent the attack on 5'-position in the reaction of *talo*-nucleoside *V* with *I*. Owing to the absence of substituents on $C_{(5')}$ the pseudorotation about $C_{(4')}-C_{(5')}$ bond in arabinoside *II* should be less hindered and therefore the 5'-hydroxyl group should be more accessible for the reagent. The product of the primary attack, however, should exhibit preferential orientation of the OR similar to the rotamer *B*, which is suitable for 3',5'-cyclisation.

EXPERIMENTAL

R_F's refer to thin-layer chromatography on ready-for-use Silufol UV_{254} silica gel foils (Kavalier Glassworks, Votice, Czechoslovakia) in the solvent system S_1, chloroform–methanol (9 : 1). Column chromatography was performed on macroporous silica gel (produced by Service Labo-, ratory, Institute of Organic Chemistry and Biochemistry). ^{1}H-NMR spectra were recorded on the apparatus Tesla BS 467 (60 MHz) and 497 (100 MHz) in deuterium chloroform using tetramethylsilane as internal standard. Trichloroacetylcarbamoyl derivatives were prepared directly in NMR sample tube, ref.[5].

3',5'-O-(Tetraisopropyldisiloxane-1,3-diyl)cytosine Arabinoside (*IIIa*)

Cytosine arabinoside (122 mg; 0·5 mmol) was evaporated with two 2 ml portions of pyridine, pyridine (2 ml) and *I* (0·17 ml; 0·55 mmol) were added and the mixture was stirred at room temperature until the nucleoside dissolved (c. 30 min). $R_F(S_1)$ 0·0 → 0·41. After 1 h, the mixture was evaporated and the residue partitioned between chloroform (5 ml) and water (10 ml). The aqueous phase was extracted twice with the same amount of chloroform, the chloroform extracts were dried over anhydrous magnesium sulfate and evaporated. The residue was evaporated with three 10 ml portions of toluene, dissolved in chloroform (2 ml) and chromatographed on silica gel column (3 × 10 cm). The column was eluted first with chloroform (25 ml) and then with chloroform–methanol (95 : 5). The fractions were checked on TLC in S_1, appropriate fractions pooled and evaporated to give a solid foam of *IIIa* (240 mg; 98%). ^{1}H-NMR spectrum (100 MHz): $H_{1'}$ 6·21 d (6); $H_{2'}$ 4·54 dd (6, 7); $H_{3'}$ ~ 4·08; $H_{4'}$ ~ 4·08; $H_{5'}$ ~ 4·15 and 3·69 d (9); H_5 5·37 d

(8); H_6, 7·60 d (8); isopropyl groups at 1·08 (strong). 2′-O-trichloracetylcarbamoyl derivative *IIIc*: H_1, 6·25 d (6); H_2, 5·99 dd (6, 8); H_3, 4·43 t (8); $H_{4'}$, H_5, 4·0—4·24 m; H_5 8·45 d (7·5); H_6 7·53 bm; NH($CONHCOCCl_3$) 8·21 s; isopropyl groups 1·15, 1·02 and 0·97.

3′-O-(Tetraisopropyl-3-hydroxydisiloxane-1-yl)cytosine Arabinoside (*IVa*)

The compound *IIIa* (36 mg; 0·075 mmol) was dissolved in 0·2M hydrochloric acid in dioxane–water (4 : 1, 0·375 ml). After 24 h R_F (S_1) 0·41 → 0·23. The mixture was evaporated, the residue partitioned between chloroform (10 ml), methanol (10 ml) and 5% aqueous ammonium hydrogen carbonate (10 ml). The aqueous phase was extracted with another portion of chloroform (10 ml), the chloroform extracts were dried over anhydrous magnesium sulfate and evaporated to give oily *IVa* (31 mg; 82%). ^{1}H-NMR spectrum (60 MHz): H_1, 6·05; $H_{2'}$, $H_{3'}$, $H_{4'}$, H_5, m 3·8—4·5; H_5 5·65 bd (8); H_6 7·65 d (8); isopropyl groups 1·03 s (strong). Trichloracetylcarbamoyl derivative *IVd*: H_1, 6·5 d (2·5); $H_{2'}$, 5·53 d (3); $H_{3'}$, 4·8 s; $H_{4'}$, H_5, 4·3—4·8; isopropyl groups 1·1 s (strong).

2′,3′-O-(Tetraisopropyldisiloxane-1,3-diyl)-1-(6-deoxy-α-L-talofuranosyl)uracil (*VIa*)

1-(6-Deoxy-α-L-talofuranosyl)uracil (51 mg; 0·2 mmol) was evaporated with two 2 ml portions of pyridine, dissolved in pyridine (1 ml) and *I* (68 μl; 0·22 mmol) was added. After 1 h, R_F (S_1) 0·05 → 0·47. The mixture was worked up according to *IIIa* and the product purified by chromatography on silica gel column in chloroform–methanol (99 : 1). The appropriate fractions were pooled and evaporated to give crystalline *VIa* (55 mg; 55%). ^{1}H-NMR spectrum (60 MHz): H_1, 5·65 d (4); $H_{2'}$, 4·66 dd (4, 5); $H_{3'}$, 4·42 t (5); $H_{4'}$, ~ 3·95; $H_{5'}$, ~ 4·0; $H_{6'}$, ~ 1·32 d (3 H, 6·5); H_5 5·78 d (8); H_6 7·66 d (8); isopropyl groups 1·05 s (strong). 5′-O-Trichloroacetylcarbamoyl derivative *VIb*: H_1, 5·89 d (3·5); $H_{2'}$, 4·54 dd (3·5, 5); $H_{3'}$, 4·30 t (5, 6); $H_{4'}$, 4·08 dd (6, 3); $H_{5'}$, 5·26 m; $H_{6'}$, 1·52 d (6·5); H_5 5·84 bdd (8, 3); H_6 7·80 d (8); NH (base) 8·70 b (J_{NH,H_5} = 3); NH ($CONHCOCCl_3$) 8·60 s; isopropyl groups 1·15 s, 1·08 s (strong).

Acetyl Derivatives *IIIb*, *IVb* and *VIb*

Acetic anhydride (0·25 ml) was added to the solution of the 3′,5′-O-tetraisopropyldisiloxane-1,3-diyl derivative (*IIIa*, *IVa*, *VIa*; c. 20 mg) in pyridine (0·5 ml). The reactions were followed by TLC in S_1 and went to completion in 6—8 h. Methanol was added and, after 10 min, the mixture evaporated. The residue was coevaporated with five 3 ml portions of toluene to give solid foams of *IIIb* and *IVb* in quantitative yields. ^{1}H-NMR spectrum (100 MHz): *IIIb*: H_1, 6·29 d (6); $H_{2'}$, 5·75 dd (6, 8); $H_{3'}$, 4·39 t (8); $H_{4'}$, ~ 4·10; $H_{5'}$, ~ 4·10 and 3·90 m; H_5 8·10 d (7·5); H_6 7·42 d (7·5); NH 9·59; CH_3COO 1·92, 2·25; isopropyl groups 1·0, 1·12. ^{1}H-NMR spectrum (60 MHz): *IVb*: H_1, 6·42 d (3); $H_{2'}$, 5·44 dd (3, 1·5); $H_{3'}$, 4·44 bs; $H_{4'}$, ~ 4·32; $H_{5'}$, 4·32 bs; H_5 7·52 dd (8, $J_{NH,5} \neq 0$); H_6 8·0 d (8); CH_3COO 2·26, 2·10 and 1·94; isopropyl groups 1·03 (strong). Si-O-trichloroacetylcarbamoyl derivative (*IVc*): H_1, 6·38 d (3·5); $H_{2'}$, 5·38; $H_{3'}$, 4·48 bs; $H_{4'}$, $H_{5'}$, 4·32 s (3 H); H_5 7·44 d (8); H_6 7·92 d (8); CH_3COO 2·26, 2·10 and 1·94; NH($Cl_3CCONHCO$) 8·85; NH (base) 9·92; isopropyl groups 1·16, 1·08.

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