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ACTION OF NUCLEOPHILES ON 2,3'-ANHYDROTHYMIDINE: SIDE-REACTIONS INVOLVING THE POSSIBLE INTERMEDIACY OF 2,5'-ANHYDRO-1-(2-DEOXY-β-D-*THREO*-PENTOFURANOSYL)THYMINE

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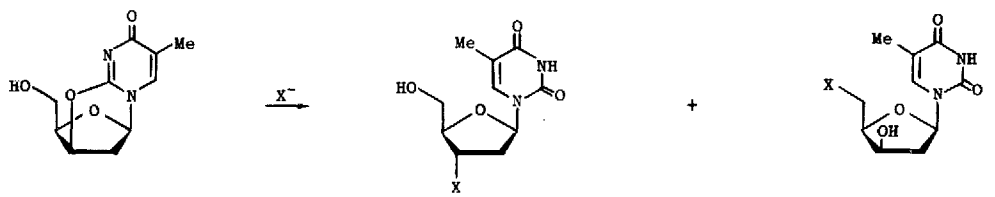
Summary: 2,3'-Anhydrothymidine (1) reacts with the sodium salt of propane-2-thiol and with sodium phenyl selenide to give 5'-substituted products [(3b) and (3c), respectively] in addition to the expected 3'-substituted 2',3'-dideoxynucleoside derivatives [(2b) and (2c)].

3'-Azido-3'-deoxythymidine (AZT, 2a) can readily be prepared, in good yield, by the action of lithium azide on 2,3'-anhydrothymidine (1) in hot *N*,*N*-dimethylacetamide (DMA) solution[1]. It therefore seemed likely that other soft nucleophiles (X^-, Scheme 1) would also react directly with (1) to give 3'-deoxythymidine derivatives (2) which were potential reverse transcriptase inhibitors.

Scheme 1



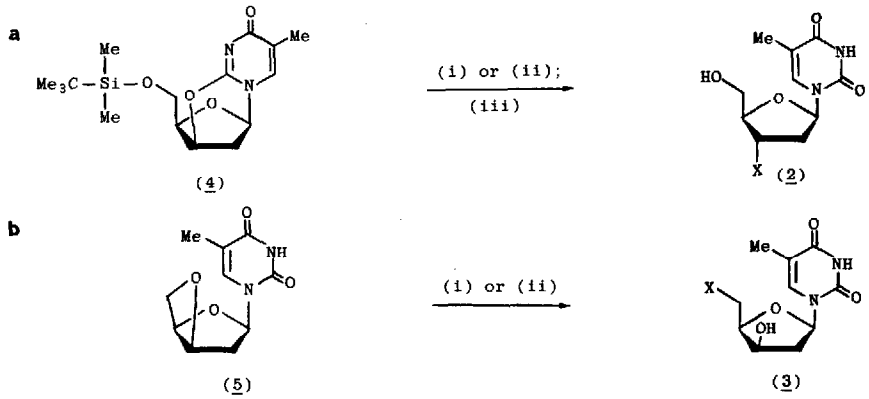
(1) (2) (3)

a; X = N_3, b; X = Me_2CHS, c; X = PhSe

We first examined the reaction between (1) and the conjugate base of an aliphatic thiol[2]. When (1) was heated with an excess of the sodium salt of propane-2-thiol in DMA solution at 100°C for 30 min, an approximately 9:1 mixture of the expected product (2b) and the isomeric 5'-deoxy-5'-(isopropylthio) derivative (3b) was obtained in 68% isolated yield. We then examined the reaction between 2,3'-anhydrothymidine (1) and sodium phenyl selenide, generated[3] by the action of sodium borohydride on diphenyl diselenide. When (1) was heated with an excess of sodium phenyl selenide in propan-2-ol solution, under reflux, for 1 hr, a *ca.* 9:1 mixture of 3'-deoxy-3'-(phenylselenenyl)thymidine[4] (2c) and the isomeric 5'-(phenylselenenyl) derivative[5] (3c) was obtained in 77% isolated yield[6].

We were unable to separate the mixture of (2b) and (3b) by TLC or by short column chromatography on silica gel. However, both compounds [(2b) and (3b)] were synthesized independently by unambiguous routes [Schemes 2a and 2b, respectively, using reagent (i)]

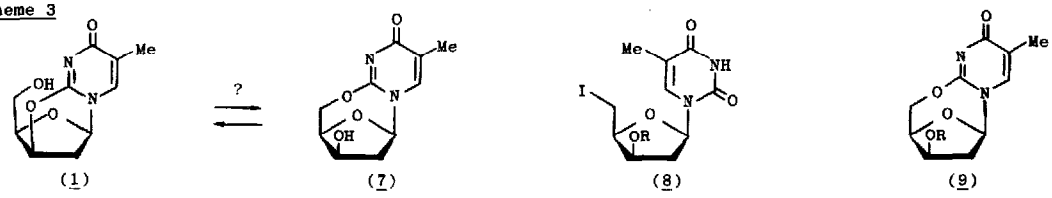
Scheme 2



Reagents: (i) Me_2CHSNa [from Me_2CHSH and NaH], $MeCONMe_2$, 100°C; (ii) PhSeNa [from $(PhSe)_2$ and $NaBH_4$ in Me_2CHOH], reflux; (iii) Et_4NF, MeCN, RT.

and were isolated as isomerically and analytically pure crystalline solids[7], m.p.s 95° and 115°C, respectively, in 61 and 65% yields. All of the resonance signals in the combined ^1H and ^{13}C-NMR spectra of (2b) and (3b) were present in the corresponding spectra of the isomeric mixture obtained [Scheme 1] by the action of sodium propane-2-thiolate on unprotected 2,3'-anhydrothymidine (1). Although we were able to effect a partial separation of (2c) and (3c) by short column chromatography, both of the latter compounds[4,5] were again synthesized by unambiguous routes [Schemes 2a and 2b, respectively, using reagent (ii)] in satisfactory yields. The composition of the mixture of products obtained [Scheme 1] by the action of sodium phenyl selenide on unprotected 2,3'-anhydrothymidine (1) was again confirmed by ^1H and ^{13}C-NMR spectroscopy.

Scheme 3

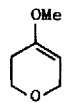


a; R = H, b; R = $MeOCH_2$-C(=O)-, c; R = 4-methoxytetrahydropyran-4-yl (Mthp), d; R = 9-phenylxanthen-9-yl (Px), e; R = $Me_3CSi(Me)_2$-

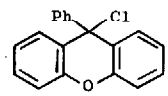
Despite the successful one-step conversion[1] of unprotected 2,3'-anhydrothymidine (1) into AZT (2a) [Scheme 1], it would seem from the above results that it is usually advisable to protect the 5'-hydroxy function of (1) [as in (4), Scheme 2a] and other related 2,3'-anhydronucleosides before carrying out nucleophilic substitution reactions at C-3'.

The most likely explanation for the formation of 5'-substituted products (3) is that, under the reaction conditions, 2,3'-anhydrothymidine (1) is partially converted into the isomeric 2,5'-anhydro-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (7) which would be expected readily to undergo nucleophilic attack at C-5'. We therefore set out to undertake the synthesis of (7) in order to examine its possible conversion into (1) and *vice versa* [Scheme 3].

When (5)[8] was heated, under reflux, with an excess of sodium iodide in glacial acetic acid solution for 30 min, the iodo-compound (8a) was obtained and isolated as a crystalline solid, m.p. 141°C, in 85% yield. The latter compound (8a) was treated with methoxyacetic anhydride in pyridine solution and the resulting 3'-*O*-methoxyacetate (8b) was heated with an excess of silver acetate[9] in acetonitrile solution to give the corresponding 2,5'-anhydronucleoside derivative[10] (9b) as a crystalline solid, m.p. 232°C, in 50% overall yield based on (8a). When (9b) was stirred in *ca.* 2.5 M-methanolic ammonia solution at room temperature for 15 min, 2,3'-anhydrothymidine (1) was obtained as a crystalline solid in 93% isolated yield. None of the isomeric 2,5'-anhydronucleoside (7) could be detected in the products. It is therefore clear that the latter compound (7) isomerizes readily under mildly basic conditions to give 2,3'-anhydrothymidine (1), and that the putative equilibrium between (1) and (7) [Scheme 3] lies very much to the left.



(10)



(11)

The 2,5'-anhydronucleoside (7) also appears to be unstable under mildly acidic conditions. Treatment of (8a) with 5,6-dihydro-4-methoxy-2*H*-pyran[11] (10) in the presence of toluene-4-sulphonic acid in dichloromethane solution gave (8c) which was also cyclized by heating it with an excess of silver acetate in acetonitrile solution. The product (9c) was isolated as a crystalline solid, m.p. 225°C, in 32% overall yield based on (8a). When a solution of (9c) in acetic acid-water (3:1 v/v) was allowed to stand at room temperature for 2 hr, 2,3'-anhydrothymidine (1) was obtained as the sole detectable nucleoside product and was isolated as a crystalline solid in 75% yield.

Finally, the 3'-*O*-(9-phenylxanthen-9-yl) derivative (9d) of the 2,5'-anhydronucleoside (7) was prepared by allowing (8a) to react with 9-chloro-9-phenylxanthene[12] (11) in pyridine solution and then heating the product (8d) with an excess of silver acetate in acetonitrile; (9d) was isolated as a crystalline solid in 41% yield based on (8a). When the latter compound (8a) was treated with *ca.* 2 mol. equiv. of t-butyldimethylsilyl trifluoromethanesulphonate in tetrahydrofuran solution at 0°C for 30 min, the 3'-*O*-(t-butyldimethylsilyl) derivative (9e) of (7) was obtained as the sole product and was isolated in 86% yield. On the other hand, when (9d) was treated first with a relatively large excess each of trifluoroacetic acid and redistilled pyrrole[13] in dichloromethane solution at 0°C

for 15 min, and the products then immediately allowed to react with an excess each of t-butylchlorodimethylsilane and imidazole at room temperature for 30 min, 5'-*O*-(t-butyldimethylsilyl)-2,3'-anhydrothymidine (4) was obtained as the sole detectable nucleoside product, and was isolated in 53% yield. None of the isomeric 2,5'-anhydronucleoside derivative (9e) was detected in the products.

A possible rationalization of the above experiments starts with the assumption that the reaction involving t-butyldimethylsilyl trifluoromethanesulphonate leads at most to free 2,5'-anhydro-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (7) as a transient intermediate. When, however, the latter compound (7) is formed either under basic conditions [i.e. by treating its 3'-*O*-methoxyacetate (9b) with ammonia in methanol solution] or acidic conditions [i.e. by treating its 3'-*O*-(4-methoxytetrahydro-2*H*-pyran-4-yl) derivative (9c) with aqueous acetic acid or its 3'-*O*-(9-phenylxanthen-9-yl) derivative (9d) with trifluoroacetic acid and pyrrole in dichloromethane solution], it must be assumed that it rapidly isomerizes to 2,3'-anhydrothymidine (1). The question then arises, that if (7) is rapidly converted into (1), why the latter compound (1) reacts with sodium propane-2-thiolate and sodium phenyl selenide [Scheme 1] to give (3b) and (3c), respectively, in addition to the expected products [(2b) and (2c)]. A possible answer to this question is that nucleophilic attack occurs much more rapidly at *C*-5' of (7) than at *C*-3' of (1). The proportion of 5'-substituted product [i.e. (3b) or (3c)] obtained would then be expected to be considerably greater than the undetectable proportion of (7) present in the putative equilibrium mixture of anhydronucleosides [(1) and (7); Scheme 3].

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