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Synthesis of Pyrrolidin-1-yl Analogues of Pyrimidine Dideoxynucleosides

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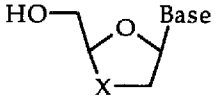
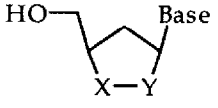
Abstract: The synthesis is described of the first members of a new class of nucleoside analogues in which the tetrahydrofuran ring is replaced by a pyrrolidine ring linked to the base through an N-N bond the pyrrolidinyl analogues of 2',3'-dideoxycytidine (**10**), uridine (**8**), and thymidine (**9**) were prepared *via* construction of the base on a 1-aminopyrrolidine (**15**).

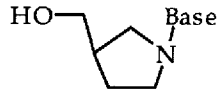
A number of molecular targets have been identified for strategies to inhibit the replication of HIV, the causative agent of AIDS, and of these the most successfully exploited so far is the virally encoded reverse transcriptase. The 2',3'-dideoxynucleosides **1** (Base = adenine, cytosine, guanine, hypoxanthine, thymine, or uracil) block HIV replication *in vitro*[1,2] by inhibition of the reverse transcriptase after intracellular conversion to their respective triphosphate esters. Of these compounds 2',3'-dideoxyinosine (**1**, Base = hypoxanthine) appears to hold the most clinical promise.[3] Members of this class of compounds are perceived to have a number of disadvantages, including lability of the glycosidic bond to acidic or enzymic (phosphorylase or hydrolase) catalysis and clinical toxicity. In an attempt to overcome some of these drawbacks, dideoxynucleoside analogues in which the terahydrofuran ring has been replaced by other 5-membered rings have been described. A carbocyclic compound **4** (Base = adenine) has weak anti-HIV activity although the corresponding 2',3'-unsaturated guanine ('carbovir') has potent activity.[4] Most recently analogues having a heteroatom in the 2'- or 3'-position have been described: an isomeric tetrahydrofuran **5** (Base = adenine, 'iso-ddA'),[5] a dioxolane **2** (Base = thymine, 'dioxolane-T'),[6] and an oxathiolane **3** (Base = cytosine, 'BCH 189')[7] have all been reported as having activity against HIV, whilst examples of tetrahydrothiophenes **6**[8] or alternative isomers **7**[9] are inactive. All these compounds, however, have a carbon atom at the 1'-position Following our interest in antiviral acyclonucleosides in which the side-chain is attached to the base by a heteroatom in an N-O[10-15] or N-N bond,[16] we report here the first members of a new series of dideoxynucleoside analogues containing a pyrrolidine ring linked to the base *via* the heteroatom (**8** - **10**).



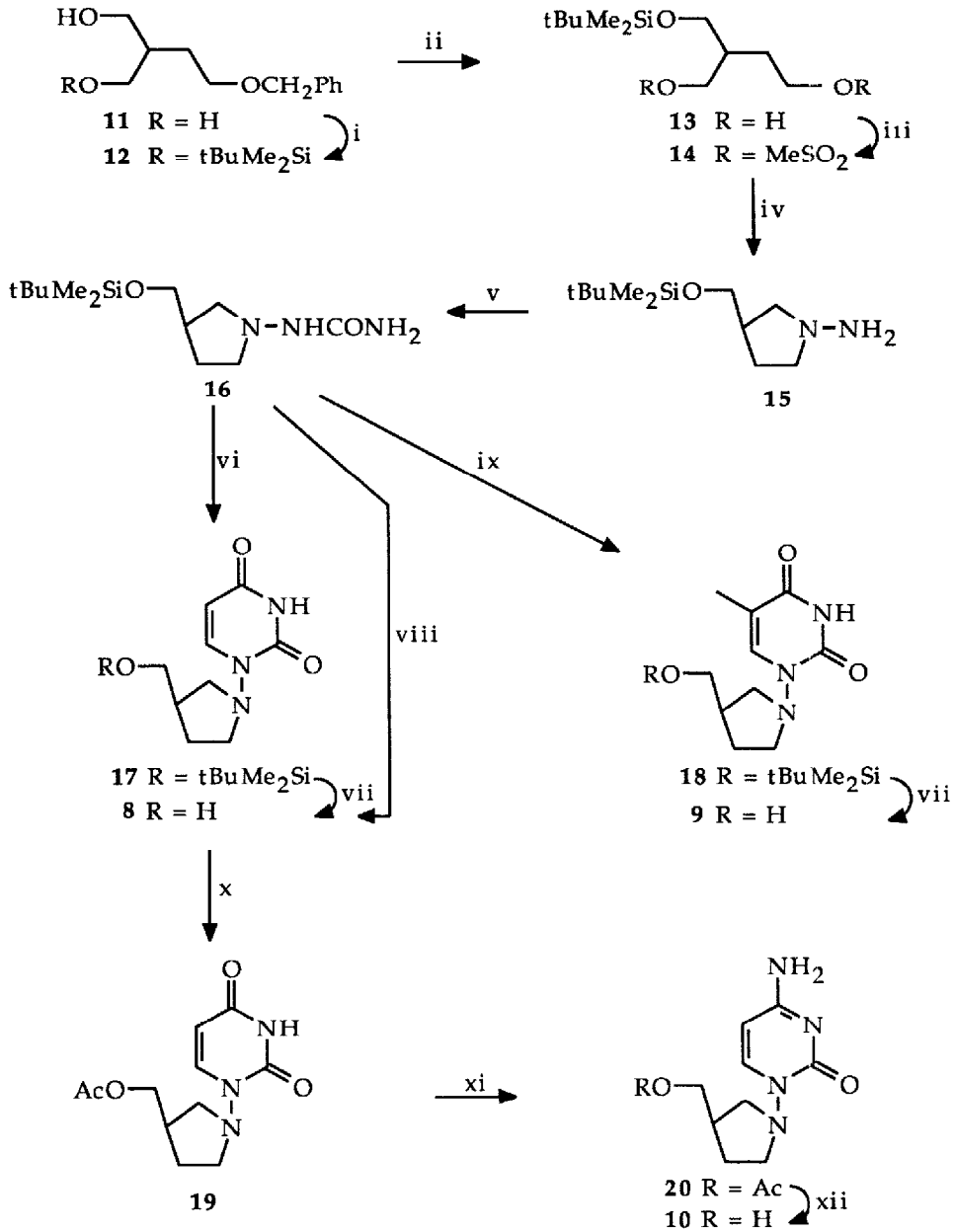
1 X = CH_2
2 X = O
3 X = S



4 X = CH_2, Y=CH_2
5 X = O, Y=CH_2
6 X = S, Y = CH_2
7 X = CH_2, Y=O



8 Base = uracil
9 Base = thymine
10 Base = cytosine



Reagents and conditions: i. NaH/THF then $tBuMe_2SiCl$; ii. H_2/Pd-C/EtOH; iii. $MeSO_2Cl/Et_3N/CH_2Cl_2$; iv NH_2NH_2/H_2O/EtOH; v. Me_3SiNCO/CH_2Cl_2; vi. $(MeO)_2CHCH_2COOMe$/NaH/DMSO/Δ; vii 80% AcOH/Δ, viii. $(MeO)_2CHCH_2COOMe$/KO*t*-Bu/*t*-BuOH/Δ then HCl/MeOH/Δ; ix. $(EtO)_2CHCHMeCOOEt$/KO*t*-Bu/*t*-BuOH/Δ; x. Ac_2O/C_5H_5N; xi. $ClC_6H_4OPOCl_2$/1,2,4-triazole/C_5H_5N then NH_3/MeOH, xii. NH_3/MeOH.

The synthetic route adopted for the preparation of the pyrrolidinyl nucleoside analogues relies on the construction of the pyrimidine ring on a protected 1-aminopyrrolidine. The diol **11**[17] was monoprotected by treatment with sodium hydride followed by t-butyldimethylsilyl chloride to afford the silyl ether **12** in 81% yield. Catalytic hydogenolysis afforded the diol **13** in quantitative yield. Reaction of **13** with methanesulphonyl chloride gave the *bis*-sulphonate **14** (92% yield) and this was treated with hydrazine hydrate to afford the 1-aminopyrrolidine **15** in 71% yield. Both **14** and **15** were obtained as liquids and neither were stable to storage at room temperature overnight. Reaction of **15** with trimethylsilyl isocyanate in anhydrous dichloromethane followed by aqueous work-up afforded the urea **16** as a stable crystalline solid (65% yield).

Attempted reaction of **16** with methyl 3,3-dimethoxypropionate in ethanolic sodium ethoxide was not successful but by changing the base/solvent to sodium hydride in dimethylsulphoxide, the uracil **17** was obtained in 19% yield. Deprotection of **17** with 80% acetic acid at 70°C afforded the dideoxyuridine analogue **8** in 73% yield.[18] The optimum base for the heterocyclic ring closure appeared to be potassium t-butoxide in t-butanol, although this did not result in complete elimination to the double bond. However, the use of t-butoxide followed by extended heating with methanolic HCl gave **8** directly in 36% yield The urea **16** did not react with the alternative uracil synthon, methyl propiolate, under any of these conditions.

Condensation of **16** with ethyl 3,3-diethoxy-2-methylpropionate afforded **18** which on deprotection with 80% acetic acid afforded the thymine nucleoside analogue **9**.[19] Attempted formation of the 5-ethyluracil derivative by a similar reaction was unsuccessful.

To obtain the cytosine derivative, the uracil **8** was protected by reaction with acetic anhydride in pyridine, giving the acetate **19** in 72% yield. Treatment of **19** with 4-chlorophenyl phosphorodichloridate and 1,2,4-triazole followed by ammonia gave the protected cytosine **20** in 51% yield. Deprotection of **20** with methanolic ammonia afforded the dideoxycytidine analogue **10** in 91% yield.[20]

The pyrrolidinyl nucleosides all showed a distinctive pattern for the ^{1}H n.m.r. signals of the pyrrolidine moiety. Complete assignment was made on the basis of COSY and nOe experiments at 270MHz. The pyrrolidine 4'-H signal at 1.5 ppm and the 2'-H signal at 3.0 ppm are due to the hydrogens on the same side of the pyrrolidine ring as the hydroxymethyl group but the two 5'-H signals were not separated. Irradiation of the 3.0 ppm signal of **10** produced an nOe enhancement of the 6-H signal; thus, although the pyrrolidine nucleosides presumably exist as a mixture of α and β forms due to inversion at the pyrrolidinyl nitrogen, a significant proportion is in the anti-β conformation characteristic of the natural nucleosides. Compounds **8** - **10** prepared in this way are racemic; synthesis of enantiomers will be reported in a subsequent publication.

The antiviral activity of these compounds will be disclosed elsewhere.

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18. Analytical data for **8**: m.p. 143-146°C; λ_{max} (H_2O) 265 (ε 9,070)nm; ν_{max} (KBr) 3470, 3050, 1695, 1680, and 1620cm^{-1}; δ_H [$(CD_3)_2SO$] 1.53 (1H, m, 4'-H), 1.87 (1H, m, 4'-H), 2.33 (1H, septet, *J* 7.4Hz, 3'-H), 3.02 (1H, dd, *J* 6.7 & 8.4Hz, 2'-H), 3.2-3.4 (5H, m, 2'-H, 2x 5'-H and CH_2O), 4.62 (1H, t, *J* 5.1Hz, D_2O exchangeable, OH), 5.43 (1H, d, *J* 8.0Hz, 5-H), 7.61 (1H,d, *J* 8.0Hz, 6-H), and 11.27 (1H, s, D_2O exchangeable, 3-H) (Found: C, 51.09; H, 6.24; N, 19.61%. $C_9H_{13}N_3O_3$ requires C, 51.18; H, 6.20; N, 19 89%).
19. Analytical data for **9**: m.p. 125-127°C; λ_{max} (H_2O) 270 (ε 9,380)nm, ν_{max} (KBr) 3470, 1700, and 1685cm^{-1}; δ_H [$(CD_3)_2SO$] 1.53 (1H, m, 4'-H), 1.72 (3H, s, CH_3), 1.87 (1H, m, 4'-H), 2.32 (1H, septet, *J* 7.4Hz, 3'-H), 3.01 (1H, dd, *J* 6.7 & 8.1Hz, 2'-H), 3.2-3.4 (5H, m, 2'-H, 2 x 5'-H and CH_2O), 4.62 (1H, t, *J* 5.2Hz, D_2O exchangeable, OH), 7.53 (1H, s, 6-H), and 11.25 (1H, s, D_2O exchangeable, 3-H) (Found: C, 53.09; H, 6.69; N, 18.61%. $C_{10}H_{15}N_3O_3$ requires C, 53.32; H, 6.71; N, 18.66%).
20. Analytical data for **10**: m.p. 200-203°C; λ_{max} (H_2O) 272 (ε 8,230)nm, ν_{mx} (KBr) 3340, 3190, 1655, 1635, 1520, 1490, and 1470cm^{-1}; δ_H [$(CD_3)_2SO$] 1.53 (1H, m, 4'-H), 1.86 (1H, m, 4'-H), 2.32 (1H, septet, *J* 7.2Hz, 3'-H), 3.04 (1H, dd, *J* 6.9 & 8.0Hz, 2'-H), 3.2-3.4 (5H, m, 2'-H, 2 x 5'-H and CH_2O), 4.58 (1H, t, *J* 5.2Hz, D_2O exchangeable, OH), 5.54 (1H, d, *J* 7.4Hz, 5-H), 7.02, 7.07 (2H, 2x br s, D_2O exchangeable, NH_2), and 7.51 (1H, d, *J* 7.2Hz, 6-H) (Found: C, 51.48; H, 6.71; N, 26.76%. $C_9H_{14}N_4O_2$ requires C, 51.42; H, 6.71; N, 26.65%).

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