Model Reactions in the Pseudonucleoside Series (1)

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A series of pseudonucleoside analogs has been prepared from the base-catalyzed condensation of methyl 3,3-dimethoxy-2-(tetrahydrofuran-2-yl)propionate with urea and thiourea, followed by cyclization(s) with acid, bromine and peroxyformic acid. Some of their reactions which lead to other model pseudonucleosides are reported.

J. Heterocyclic Chem., 13, 929 (1976).

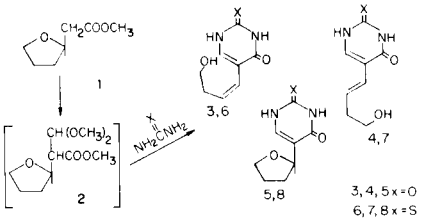
Sir:

As part of our program on the synthesis of pseudonucleosides, their analogs, and the specific intramolecular interactions which affect the physicochemical properties of pseudouridines (2), we prepared the compounds described here. The synthetic approaches developed should be applicable to the preparation and interconversions of other desired 2'-hydroxy- or 2'-deoxypentafuranosylpseudonucleoside derivatives.

The pseudonucleoside analogs were obtained from the methyl ester of 2-(tetrahydrofuran-2-yl)acetic acid (**1**, Scheme I) *via* the condensation method we have previously reported (3) for several 5-substituted uracils.

The esterification of 2-(tetrahydrofuran-2-yl)acetic acid with dry methanol in the presence of Dowex 50 (H^+) gives the methyl ester **1** (bp 92°/19 Torr) in a yield better than 90% (Scheme I); nmr (deuteriochloroform): δ 2.27 (q, 1, J_{AB} = -15.2 Hz, J_{AX} = 6.3 Hz, -C*H*(H)-CO_2CH_3), 2.45 (q, 1, J_{AB} = -15.2 Hz, J_{BX} = 6.9 Hz, -CH(*H*)-CO_2CH_3), 3.52 (s, 3, -OCH_3), 4.1 (m, 1, "anomeric" H). Formylation of this ester in benzene as described (3) gives the acetal **2**. The pmr spectrum is consistent with that structure although correct elemental analysis was not obtained.

Scheme I

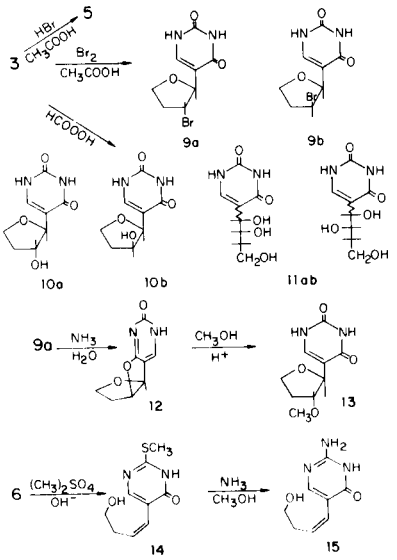


The base catalyzed (sodium methoxide) condensation of **2** with urea or thiourea produces, respectively, the 5-substituted *cis*- and *trans*-5-(4-hydroxy-1-butenyl)- and the expected 5-(tetrahydrofuran-2-yl)-derivatives of uracil (**3**,**4**,**5**) and thiouracil (**6**,**7**,**8**). In each case, the mixture is resolved by a combination of chromatography first on Dowex 50 (H^+, water) and then on silica gel (benzene-ethyl acetate-methanol, 8:1:1); **3**, m.p. 245-246° (ethanol): uv λ max (water): 277 nm (6.6 x 10^3), 257.5 nm (4.7 x 10^3); nmr (4) (DMSO-d_6): δ 6.09 [d, 1, $J_{1',2'(cis)}$ = 11.6 Hz, $H_{1'}$], 7.46 (s, 1, H_6); **4**, m.p. 239-241°, (ethanol); uv λ max (water): 290 nm (7.2 x 10^3), 266.5 nm (4.9 x 10^3); nmr (DMSO-d_6): δ 6.05 (d, 1, $J_{1',2'}$ (*trans*) = 15.9 Hz, $H_{1'}$), 7.45 (s, 1, H_6); **5**, m.p. 243-245° (methanol); uv λ max (water): 263 nm (7.7 x 10^3); nmr (DMSO-d_6): δ 4.58 [t, 1, $(J_{1',2'})_{cis}$ + $(J_{1',2'})_{trans}$ = 12.8 Hz, $H_{1'}$], 7.17 (s, 1, H_6); **6**, m.p. 205-206° (ethanol); uv λ max (water): 307 nm (15.0 x 10^3), 284 nm (14.6 x 10^3); nmr (DMSO-d_6): δ 6.18 (double d, 1, $J_{1',2'}$ = 11.9 Hz, $J_{1',3'}$ = 0.8 Hz, $H_{1'}$), 7.50 (s, 1, H_6); **7**, m.p. 225-226° (ethanol); uv λ max (water): 314 nm (17.5 x 10^3), 290 nm (sh 16.0 x 10^3); nmr (DMSO-d_6): δ 6.10 [d, 1, $J_{1',2'}$ (*trans*) = 15.9 Hz, $H_{1'}$], 7.48 (s, 1, H_6); **8**, m.p. 242-244° (ethanol); uv λ max (water): 278.5 nm (16.1 x 10^3); nmr (DMSO-d_6): δ 4.61 [t, 1, $(J_{1',2'})_{cis}$ + $(J_{1',2'})_{trans}$ = 12.2 Hz, $H_{1'}$], 7.16 (s, 1, H_6).

In the reaction with urea the *cis*-olefin **3** is the major product while the *trans*-isomer **4** and the tetrahydrofuran derivative **5** are isolated in minor amounts. With thiourea the major product is the tetrahydrofuran derivative **8** followed by the *trans*-olefin **7**. In this case, the *cis*-isomer

6 is obtained in minor amounts. These results confirm our earlier conclusions regarding the general mechanism of the reaction of 3-alkoxy-2-dialkoxymethyl-esters with ureas (3). The production of 5-vinyl derivatives of pyrimidines from such condensations is now established. This finding should be of importance to the synthesis of 2'-deoxy-pseudonucleosides from glycosyl-intermediates analogous to **1** and **2**.

Scheme II



In hydrogen bromide-acetic acid **3** undergoes, in part, cyclization to the 5-(tetrahydrofuran-2-yl)uracil, **5** (Scheme II). In a similar reaction with bromine in acetic acid, the anomeric 5-(3-bromotetrahydrofuran-2-yl)uracils, **9a**, [m.p. 223-227° dec. (methanol); nmr (DMSO-d_6): δ 4.88 (double d, 1, $J_{1',6}$ = 0.9 Hz, $J_{1',2'}$ = 2.8 Hz, $H_{1'}$), 7.27 (d, 1, $J_{1',6}$ = 0.9 Hz, H_6)]; and **9b** [m.p. 236-237° (methanol); nmr (DMSO-d_6): δ 4.63 (double d, 1, $J_{1',6}$ = 1.2 Hz, $J_{1',2'}$ = 3.1 Hz, $H_{1'}$), 7.25 (d, 1, $J_{1',6'}$ = 1.2 Hz, H_6)] are formed in high yield. Oxidation of **3** with peroxyformic acid leads to the anomeric 5-(3-hydroxytetrahydrofuran-2-yl)uracils, **10a** [m.p. 249.5-251° (methanol); uv λ max (water): 262.5 nm (7.9 x 10^3); nmr (DMSO-d_6): δ 4.42 (double d, 1, $J_{1',6}$ = 1.2 Hz, $J_{1',2'}$ = 2.1 Hz, $H_{1'}$), 7.13 (d, 1, $J_{1',6}$ = 1.2 Hz, H_6)] and **10b** [m.p. 236.5-237° (methanol); λ max (water): 263.5 nm (7.5 x 10^3); nmr (DMSO-d_6): δ 4.45 (double d, 1, $J_{1',6}$ = 1.1 Hz, $J_{1',2'}$ = 3.1 Hz, $H_{1'}$), 7.11 (d, 1, $J_{1',6}$ = 1.1 Hz, H_6)], as well as to the isomeric triols, **11a,b**. The latter triols have not been resolved but the mixture obtained is crystalline [m.p. 159-161.5° (methanol)].

In concentrated ammonia, **9a** is converted rapidly to the model "cyclo" pseudonucleoside, **12** [m.p. 220-221° (methanol); uv λ max (water): 277 nm (4.6 x 10^3); nmr (DMSO-d_6): δ 5.41 (s, 1, $H_{1'}$), 7.97 (s, 1, H_6)]. This reaction is consistent with a *trans*-configuration for **9a**. The "cyclo" derivative **12** is stable in refluxing dry methanol but upon addition of one equivalent of *p*-toluenesulfonic acid to this system, **12** is converted to the 5-(3-*trans*-methoxytetrahydrofuran-2-yl)uracil **13** [m.p. 254-255.5° (methanol); uv λ max (water): 263.5 nm (7.9 x 10^3); nmr (DMSO-d_6): δ 4.60 (double d, 1, $J_{1',6}$ = 1.2 Hz, $J_{1',2'}$ = 1.4 Hz, $H_{1'}$), 7.20 (d, 1, $J_{1',6}$ = 1.2 Hz, H_6)] (5) and some unidentified fluorescent material. The structural assignments for the anomeric configurations of **9a**, **10a**, **13** and **9b**, **10b** are made on the basis of correlations and differences regarding the $J_{1',2'}$ values (2.8, 2.1 and 1.4 Hz for **9a**, **10a** and **13** respectively *vs* 3.1 Hz for **9b** or **10b**) and the uv properties of their monoanionic species. With respect to the latter, it is noteworthy that **9a**, **10a** and **13** resemble β-pseudouridine while **9b** and **10b** are like α-pseudouridine (6).

The methylation of the vinylic-2-thiouracil, **6**, with dimethylsulfate in basic aqueous solution, proceeds smoothly to give the expected methylmercapto derivative **14** [m.p. 171-172° (methanol); nmr (DMSO-d_6): δ 6.22 (d, 1, $J_{1',2'(cis)}$ = 11.9 Hz, $H_{1'}$), 7.91 (s, 1, H)]. This product is aminated with a saturated (0°) solution of methanolic ammonia in a sealed vessel at 100° to the corresponding isocytosine, **15** [m.p. 221-224° (ethanol); nmr (DMSO-d_6): δ 6.14 (d, 1, $J_{1',2'(cis)}$ = 11.9 Hz, $H_{1'}$)], 7.64 (s, 1, H_6).

All new compounds showed the proper elemental analyses.

Acknowledgement.

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REFERENCES AND NOTES

(1) This investigation was supported in part by Public Health Service Research Grants No. CA-16191, CA-17085 and CA-08748 from the National Cancer Institute.

(2) For our latest report on this subject, see A. J. Playtis and J. D. Fissekis, *J. Org. Chem.*, **40**, 2488 (1975).

(3) J. D. Fissekis and F. Sweet, *ibid.*, **38**, 1963 (1973).

(4) In some cases, $J_{1',2'}$ was determined by irradiating at the H_6 frequency to eliminate the additional $J_{1,6}$ coupling.

(5) Comparable examples in the "cyclonucleoside" series have been recorded. For a review see J. J. Fox, *Pure Appl. Chem.*, **18**, 223 (1969).

(6) R. W. Chambers, *Prog. Nucleic Acid Res. Mol. Biol.*, **5**, 349 (1966).