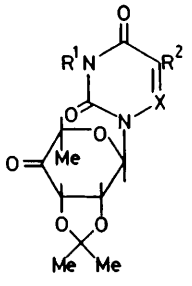
Enol Acetates from Oxo-nucleosides: a New, Mild, Regioselective Method

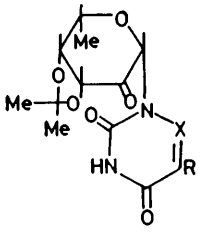
By MICHEL BESSODES,† ABRAHAM OLLAPALLY, and KOSTAS ANTONAKIS*
(*Institut de Recherches Scientifiques sur le Cancer, C.N.R.S.*, 94 800 *Villejuif, France*)

Summary The reaction of some oxo-nucleosides of uracil with dimethylformamide acetals leads, after addition of acetic anhydride, to the corresponding enol acetate-nucleosides; this is the first synthesis of enol acetate-nucleosides by direct enolisation of an oxo-nucleoside.

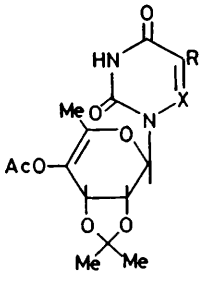
THE now well established activity of oxo-nucleosides against a variety of tumours and cancer cells[1] prompted us to investigate the synthesis of new derivatives which could be direct precursors for these compounds. We report here the first reaction of dimethyl formamide (DMF) acetals with some oxo-nucleosides. These DMF acetals are known to react readily on heating with heterocyclic compounds containing a CO–NH group, such as uracil, leading to the corresponding *N*-alkyl derivative.[2]



(1) R^1 = H, R^2 = F, X = CH
(2) R^1 = H, R^2 = H, X = N
(3) R^1 = Me, R^2 = F, X = CH



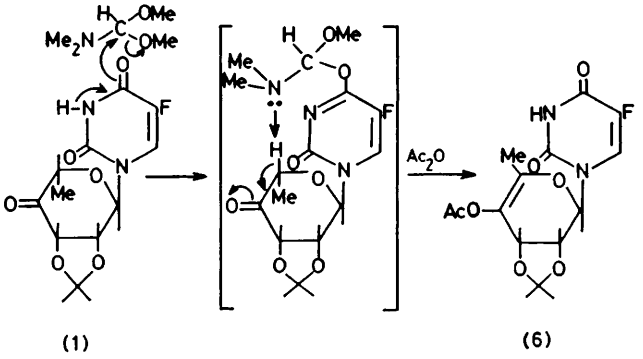
(4) R = F, X = CH
(5) R = H, X = N



(6) R = F, X = CH
(7) R = H, X = N

Typically, when a solution of the oxo-nucleosides (**1**)—(**5**) (1 mmol) in ether was treated with DMF diethyl acetal (1·5 mol. equiv.) at room temperature no alkylation occurred. However, enolisation of the oxo group was observed for compounds (**1**) and (**2**). Treatment of the resulting precipitates with acetic anhydride–pyridine gave the corresponding enol acetates (**6**) and (**7**) in *ca.* 60% yield. Spectral and analytical data for (**6**) and (**7**) are in accordance with the proposed structures: compound (**6**), ^{1}H n.m.r. ($CDCl_3$) δ 5·9 (d, H-1), 4·2 (q, H-2), 4·9 (d, H-3), and 1·3 (s, H-6), ε (264 nm) 10 500, m.p. 217 °C (decomp.); compound (**7**), ^{1}H n.m.r. ($CDCl_3$) δ 6·0 (d, H-1), 4·4 (q, H-2), 4·9 (d, H-3), and 1·5 (s, H-6), ε (264 nm) 8 400, m.p. 219 °C (decomp.).

These results show that this reaction is highly regiospecific. Two structural conditions were required for the enolisation of the oxo compounds: the oxo group should be in the 4′-position and a free CO–NH group should be present in the pyrimidine ring. We thus propose the mechanism shown in the Scheme. The formation of a



(1) (6)

SCHEME

† Attaché de Recherches à l'INSERM.

mixed acetal with the pyrimidine CO–NH group, in the first step, has been shown as follows: mixed acetals [detected by loss of migration in t.l.c. (EtOAc)] which have been obtained with the 4′-oxo-nucleosides (**1**) and (**2**) as well as with the 2′-oxo-nucleosides (**4**) and (**5**) revert to the starting nucleosides on adding an excess of deuteriated methanol, with n.m.r. studies of the resulting compounds showing a quantitative exchange of the H-3 proton of the pyrimidine; the u.v. spectra of the oxo-nucleosides after reaction with DMF acetal showed a displacement of absorption from 264 to 243 nm; attempts to enolise the oxo-nucleoside (**3**) failed.

Studies on molecular models of these mixed acetals showed that for the 4′-oxo-nucleosides (**1**) and (**2**) the 5′α-hydrogen of the sugar is influenced by the free orbitals of the nitrogen atom of the mixed acetal, thus allowing a mild and regiospecific enolisation of the ketone. This is not observed for the 2′-oxo-nucleosides (**4**) and (**5**).

The use of DMF acetals thus constitutes a new and interesting method for the synthesis of enol-acetates from oxo-nucleosides. All previously known methods of enol formation[3] failed with the oxo-nucleosides owing to their instability in alkaline media. These new derivatives of oxo-nucleosides promise to be important synthetic precursors of branched chain sugar nucleosides and rare sugar nucleosides. Furthermore, the study of their stability in alkaline media has shown that they can readily revert to the starting ketone; thus restoring, by a simple saponification *in vivo*, the original activity of the oxo-nucleoside.

We thank the Institut National de la Santé et de la Recherche Médicale, the N.S.F., and the NIH for partial support and Mr. R. Hurchins, Department of Chemistry, Florida A & M University, for preparation of the starting nucleosides.

(*Received, 7th March* 1979; *Com.* 229.)

[1] K. Antonakis and I. Chouroulinkov, *Biochem. Pharmacol.*, 1974, **23**, 2095; C. Aujard, Y. Moulé, E. Chany-Morel, and K. Antonakis, *ibid.*, 1978, **27**, 1037; I. Chouroulinkov and K. Antonakis, *Compt. rend.*, 1977, **273D**, 2661.
[2] J. Žemlička, *Coll. Czech. Chem. Comm.*, 1963, **28**, 1060.
[3] D. Horton and E. K. Just, *Carbohydrate Res.*, 1969, **9**, 129; S. L. Cook and J. A. Secrist, *ibid.*, 1976, **53**, C3—C6; A. Ducruix, C. Pascard-Billy, S. J. Eitelman, and D. Horton, *J. Org. Chem.*, 1976, **41**, 2652.