New Synthesis of 4′,5′ Unsaturated Nucleosides

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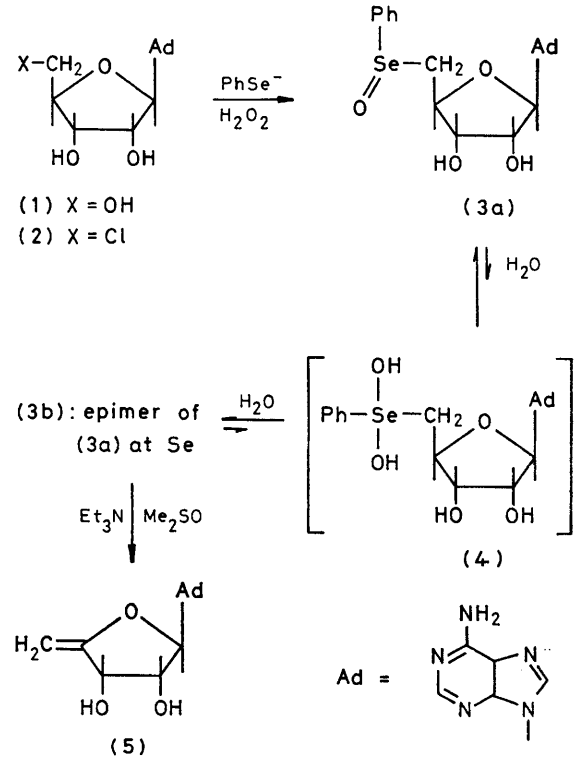
Summary 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)-adenine was synthesized by thermal fragmentation of the corresponding 5′-phenylselenoxide.

THE introduction of the exocyclic C(4′)–C(5′) double bond in the sugar unit of adenosine is a key step in the synthesis of antibiotics related to angustmycin[1] and nucleocidin.[2] These syntheses use routes which involve blocking and deblocking procedures to achieve the introduction of the double bond; generally E_2 elimination of H(4′) and a good leaving group at C(5′) (*p*-$MeC_6H_4SO_3$, $MeSO_3$, Br, or I), are used. The yields in this elimination step are limited by the instability of the starting compound and its ability to undergo nucleophilic displacement leading to N(3)–C(5′) cyclonucleosides.[3] This side reaction can be hampered by benzoylation of the 6-NH_2 group, which decreases the nucleophilicity of N(3).

We now report a new method for generating the exocyclic double bond based on the following considerations: (i) adenosine (**1**) can be specifically and quantitatively converted into 5′-chloro-5′-deoxy-adenosine (**2**),[4] a compound which is stable with respect to intramolecular cyclisation; (ii) selenoxides readily undergo *syn* elimination under very mild conditions to give the corresponding ethylenic compound.[5]

Treatment of 5′-chloro-5′-deoxy-adenosine (**2**) (90% yield from adenosine) with sodium benzene selenolate in tetrahydrofuran–hexamethylphosphoric triamide (THF–HMPT)[6] gave 5′-phenylseleno-5′-deoxyadenosine which was oxidised *in situ* by H_2O_2 to the stable crystalline selenoxide (**3a**)† (m.p. 169–171 °C; 54% yield). The n.m.r. spectrum‡ showed one set of signals indicating the presence of a single diastereoisomer. This compound is stable in boiling MeOH or EtOH but undergoes epimerisation at



selenium in water: this transformation can be easily followed by the n.m.r. spectrum (D_2O) in which there progressively appears a second set of signals assigned to the epimeric selenoxide (**3b**). After 2 h a 56:44 equilibrium

† All compounds showed satisfactory microanalytical and spectroscopic data (^1H n.m.r. and u.v.).

‡ ^1H N.m.r. (250 MHz; Me_2SO–D_2O) δ 8·3 and 8·1 (both s, 1H, 2- and 8-H), 5·96 (d, 1H, 1′-H), 4·87 (dd, 1H, 2′-H), 4·4 (m, 1H, 4′-H), 4·21 (dd, 1H, 3′-H), 3·68 (dd, 1H, 5′-H), and 3·05 (dd, 1H, 5″-H); J(1′,2′) 5·6, J(2′,3′) 4·9, J(3′,4′) 3·0, J(4′,5′) 10·6, J(4′,5″) 3·4, and J(5′5″) 11·3 Hz.

mixture is obtained. As water is necessary for this epimerisation, the hydrate form (**4**) is probably an intermediate.[7] Heating of the pure selenoxide (**3a**) in Me_2SO gives a mixture of products which is difficult to purify. However, when the selenoxide (**3a**) or the mixture of (**3a**) and (**3b**) is heated at 100 °C for 1 h in Me_2SO–H_2O (10 : 0·6) in the presence of 3 equiv. of triethylamine, the elimination product (**5**)† (m.p. 182—186 °C; lit.,[1b] m.p. 185 °C) is obtained (94% yield of isolated product following chromatography on Bio-Rad AG1-X2, OH^- form, 200—400 mesh). These observations can be rationalised by assuming that the opposite configuration of the selenium atom[8] in the selenoxides (**3a**) and (**3b**) leads to different relative orientations of the selenoxide group and H(4′), one of which is much more suitable for *syn* elimination. The presence of water in the reaction solvent is necessary for the fast epimerisation of (**3a**) to (**3b**). The high temperature needed to induce the elimination of this primary selenoxide is probably due to the presence of oxygen on C(4′).[5b] Even at this temperature the yield is high. Therefore, this method, which avoids the introduction of a good leaving group at C(5′), should prove a general one for the formation of an exocyclic double bond in other nucleosides.

We are currently investigating other methods to prepare the selenide and to bring about the elimination in order to avoid the use of HMPT which has known carcinogenic properties.

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