Formation of a Tricyclic Nucleoside from Deoxyguanosine *via* an O^6-N^1-Transposition

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The synthesis of a tricyclic deoxynucleoside by reaction of β-substituted ethanols with an activated deoxyguanosine is described. Its formation is rationnalised by an O^6-N^1-transposition.

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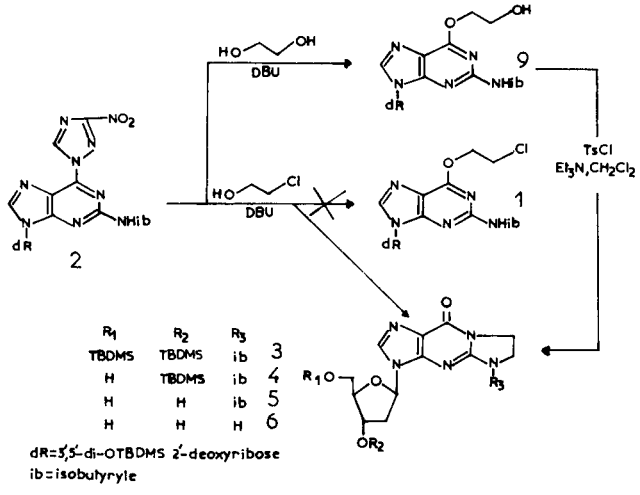
During the course of our studies on crosslinked dinucleosides [1-2] we wished to prepare O^6-(2-chloroethyl)-deoxyguanosine (**1**) which is one of the principal promutagenic structures [3] involved in DNA crosslink formation. In principle the compound should be available through direct condensation of the activated deoxyguanosine derivative **2** [2] and chloroethanol, using DBU as strong base.

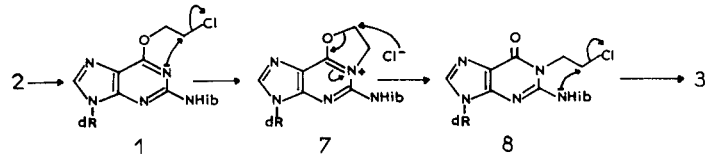


Scheme I

Accordingly, the reaction of **2** with chloroethanol (3 equivalents) in presence of DBU (2.7 equivalents) in acetonitrile gave a disilylated nucleoside **3** (70% yield) which on deblocking (tetrabutylammonium fluoride/tetrahydrofuran, rt, 1 hour and aqueous ammonia, 60°, 24 hours) yielded a new deoxynucleosidic compound **6**. Using the usual physical methods, this compound was shown [4] to be 3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5,6,7,9-tetrahydro-9-oxoimidazo[1,2-*a*]purine (Scheme I). The mass spectrometric data (FAB⁺) gave $MH^+ = 294$, $BH^+ = 178$.

The heterocyclic system of **6** is already known and has been obtained by the reaction of suitable protected guanines with glyoxal [5-6].

The probable mechanism of formation of **3** is depicted in Scheme II. Reaction of chloroethanol with the activated



Scheme II

deoxyguanosine **2** would be expected to give O^6-(2-chloroethyl) derivative **1** which could rearrange through the postulated [7] oxazolidinium intermediate **7** to the N^1-(2-chloroethyl) derivative **8**. Subsequent chlorine displacement by nucleophilic attack of the N^2 atom of deoxyguanosine would afford the protected 1,N^2-ethanodeoxyguanosine **3**. All attempts to isolate any of the postulated intermediates were unsuccessful.

However, this mechanism was corroborated by an additional experiment where we replaced the chlorine leaving group by a tosyloxy one. The O^6-(2-hydroxyethyl)deoxyguanosine derivative **9** is available from the reaction of ethyleneglycol with **2** [2] (Scheme I). Tosylation of **9** in the presence of base again gave the expected transposed 1,N^2-ethanodeoxyguanosine compound, isolated as a mixture of silylated nucleosides (**4**/**3**:32/68, 70% yield). After deprotection, each of these afforded the tricyclic derivative **6**. All attempts to chlorinate **9** resulted in unresolved complex mixtures.

It thus appears that under the conditions described above the O^6-(2-chloroethyl)deoxyguanosine derivative cannot be isolated by direct substitution of suitably activated deoxyguanosine with chloroethanol. The presence of a good leaving group (*i.e.* Cl, OTs) on the substituted O^6-ethyl chain gives rise, through transposition, to the corresponding tricyclic nucleoside **6**.

The proposed mechanism can partially account for the mutagenic effect of chloroethylnitrosoureas. It is believed [7] that the oxazolidinium intermediate **7** generates DNA interstrand crosslinks, mainly responsible for the cytotoxicity of nitrosoureas [8]. Alternatively, it can competitively lead to the formation of an imidazolidinylpurine ring

whose mutagenicity has been previously reported [9].

Acknowledgments.

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[4] Compound **6**: ^{1}H-nmr (deuterium oxide): 200 MHz δ ppm 7.85 (s, 1H, H_2), 6.13 (t, 1H, J = 7.5 Hz, $H_{1'}$), 4.53 (m, 1H, $H_{3'}$), 4.09 (m, 3H, $H_{4'}$, CH_2N), 3.73 (m, 4H, $H_{5'5''}$,CH_2N), 2.53 (m, 2H, $H_{2'2''}$); uv (95% ethanol): λ max nm 252 (ϵ 10680), λ infl nm 275 (ϵ 5125), λ min nm 225 (ϵ 2660); (0.1*N* hydrochloric acid): λ max nm 255, λ infl nm 277, λ min nm 234; (0.1*N* potassium hydroxide): λ max nm: 252, λ infl nm 272, λ min nm 229.

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