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A DIRECT METHOD FOR THE ALKYLATION OF ADENOSINE NUCLEOSIDES AT POSITION 8.

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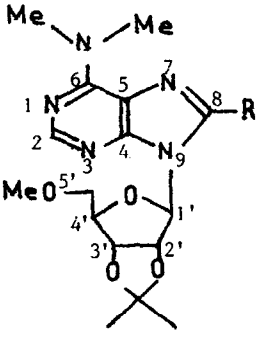
Abstract — Alkylation of adenosine derivatives at carbon 8 can be conveniently achieved by lithiation followed by reaction with an alkyl halide.

Selective methods for the direct modification of purine nucleoside derivatives are surprisingly few in number. As part of a more general programme directed towards the synthesis of nucleoside analogues as inhibitors of methyl transferase[1], we have investigated the metalation of several adenosine derivatives. The mutagenic activity of alkylating agents on nucleic acids and the isolation of methylated purine nucleosides as minor components of transfer ribonucleic acid have already prompted numerous synthetic investigations on alkylation[2].

We conceived that lithiation of a suitably protected derivative of adenosine might lead to substitution at carbon - 8 of the purine ring system.

Initially, in order to establish the feasibility of a carbon alkylation process, we examined the reaction of the fully protected derivative (1).



(1) R = H

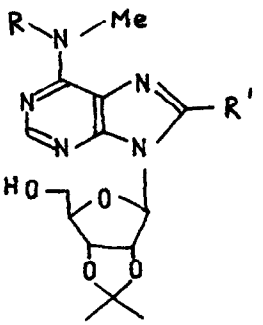
(2) R = Me

(3) R = Et

Addition of butyllithium (3 equivalents) to (1) in tetrahydrofuran cooled to -78°C, followed by quenching with an excess of methyl iodide and allowing to warm to room temperature, gave N^6, N^6-dimethyl - 8-methyl - 5'-O-methyl - 2',3'-isopropylideneadenosine (2) in 88% yield. $[\alpha]_D$ - 23° (c 0.82, EtOH) ; λ_{max}^{EtOH} 273 nm (ε 20,040); m/e, 363, (M^+) ; δ ($CDCl_3$) 1.60 and 1.40 (2 x 3H, s, $(CH_3)_2$ C<) ; 2.57 (3H, s, 8-Me), 3.23 (3H, s, OMe), 3.43 (6H, s, $(CH_3)_2N$-), 3.50 (2H, d, H-5'), 4.23 (1H, m, H-4'), 5.03 (1H, dd, H-3'), 5.57 (1H, d-d, H-2'), 5.90 (1H, d, H-1'), 8.07 (1H, s, H-2).

The corresponding ethyl derivative (3) could also be prepared either by using iodoethane (51%) or by metalation of the 8-methyl adenosine derivative (2) and subsequent reaction with methyl iodide (48%). $[\alpha]_D$ - 15° (c 2.4, EtOH); λ_{max}^{EtOH} 275 nm, (ε 19,200); δ($CDCl_3$) , 1.37 (3H, t, $\underline{CH_3}$-CH_2), 1.60 and 1.40 (2 x 3H, s, $(CH_3)_2$ C<), 2.90 (2H, q, $CH_3\underline{CH_2}$), 3.27 (3H, s, OMe), 3.47 (6H, s, $(CH_3)_2$N-), 3.53 (2H, d, H-5'), 4.27 (1H, m, H-4'), 5.10 (1H, d-d, H-3'), 5.63 (1H, d-d, H-2'), 6.00 (1H, d, H-1'), 8.17 (1H, s, H-2) .

We have also studied the application of this sequence to N^6-methyl-2',3'-isopropylidene-adenosine (4), resulting in the isolation of the 8-methyl derivative (5) in 35% yield. (λ_{max}^{EtOH} 276 nm, (ε 16,500) ; m/e 349 (M^+) ; δ($CDCl_3$) 1.63 and 1.37 (2 x 3H, s, $(CH_3)_2$ C) , 2.53 (3H, s, 8-Me), 3.43 (6H, s, $(CH_3)_2$N-), 3.77 (2H, d-d, H-5'), 4.40 (1H, s, H-4'), 5.02 (1H, s, H-3'), 5.10 (1H, m, H-2'), 5.73 (1H, d, H-1'), 8.30 (1H, s, H-2). Significantly, under these conditions, the methyl ether (2) was formed only as a minor by product (7%).



(4) R = R' = H

(5) R = R' = Me

These preliminary results indicate the potential for direct alkylation of adenosine nucleosides.

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References

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