Conversion of Guanosine into its N^2-Methyl Derivative

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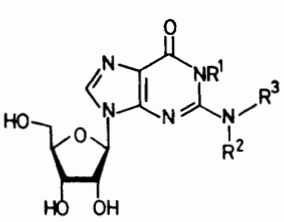
Summary N^2-Methylguanosine (**1c**) may be prepared in satisfactory yield by treating the protected guanosine derivative (**5a**) with diazomethane and then removing the protecting groups; (**5a**), which readily reacts with dimethylamine to give (**5c**), may be prepared from (**4a**) in good yield.

IT is believed[1] that the *N*-methylated minor nucleosides which occur widely in transfer ribonucleic acids (tRNA) are formed by enzyme-promoted methylation of the base residues at the macromolecular level. However, of the four simple *N*-methyl derivatives of guanosine {1-methyl-, N^2-methyl-, N^2N^2-dimethyl-, and 7-methyl-guanosines [(**1b**), (**1c**), (**1d**), and (**2**), respectively]} found[2] in tRNA, only (**1b**) and (**2**) have been prepared directly[3] by the methylation of guanosine (**1a**). N^2-Methyl- and N^2N^2-dimethyl-guanosines (**1c** and **1d**, respectively) have been prepared from 5-amino-1-β-D-ribofuranosyl-4-imidazolecarboxamide[4] (**3**) and also from comparatively inaccessible derivatives of 9-β-D-ribofuranosyl-2-fluoropurine.[5] We now report a convenient method for the preparation of N^2-methylguanosine (**1c**) by the direct methylation of a protected guanosine derivative.

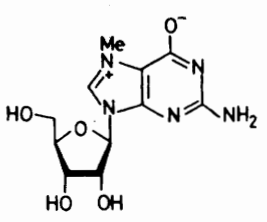
Reaction between $N^2O^{2'}O^{3'}O^{5'}$-tetrabenzoylguanosine[6] (**4a**) and an excess of methanesulphonyl chloride in the presence of triethylamine in dichloromethane solution gives its 6-*O*-mesyl derivative (**5a**), which may be isolated as a colourless crystalline compound,† m.p. 156—157 °C, in 75% yield. The structure assigned to (**5a**) is based on the following evidence. Reaction between (**5a**) and *ca.* 3 mol. equiv. of 20% methanolic dimethylamine in dioxan solution to give (**5c**) is complete within 15 min at 20 °C. Treatment of the latter compound (**5c**), which may be isolated as a crystalline solid, m.p. 157 °C, in 85% yield, with 33% alcoholic methylamine for 8 days‡ at 20 °C gives (**6**) in 92% yield. The product obtained is identical to authentic material prepared by treating 9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2-amino-6-chloropurine[7] with methanolic dimethylamine.

When a solution of (**5a**) in dichloromethane–methanol (10 : 3 v/v) is allowed to react with *ca.* 4—5 mol. equiv. of ethereal diazomethane for 90 min at 0 °C and then for 180 min at 20 °C, a mixture of (**5b**), a second methylation product believed to be (**5**; R^1 = Me, R^2 = OMe; *ca.* 12%), and some unchanged starting material (**5a**; *ca.* 17%) is obtained. The latter compound (**5a**) is removed by chromatography and the methylated products are then treated with 0·5M-K_2CO_3 in water–dioxan (1 : 1 v/v) for 45 min at 20 °C. Fractionation of the products gives $N^2O^{2'}O^{3'}O^{5'}$-tetrabenzoyl-N^2-methylguanosine (**4b**) as a glass in 53% yield. When (**4b**) is treated with 33% alcoholic methylamine for 16 h at 20°C, N^2-methylguanosine (**1c**), m.p. 235 °C (decomp.), is obtained in 90% yield. The product obtained is identical (^{1}H n.m.r., u.v., and mass spectra; t.l.c. in several systems) to authentic material.

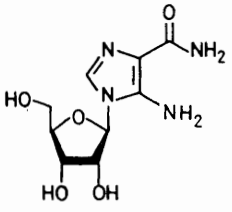
We are unaware of the previous use of an *O*-mesyl protecting group for base transformations in nucleoside or indeed in any other branch of heterocyclic chemistry. Furthermore, nucleophilic displacement of mesylate ion from (**5a**) occurs with exceptional ease thereby suggesting a general procedure for carrying out transformations such as (**4a**) → (**5c**) in heterocyclic chemistry.



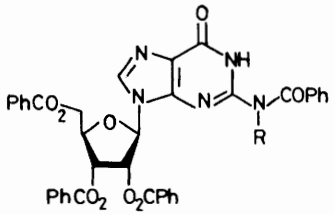
(1) a; $R^1 = R^2 = R^3 = H$
b; $R^1 = Me$; $R^2 = R^3 = H$
c; $R^1 = R^2 = H$; $R^3 = Me$
d; $R^1 = H$; $R^2 = R^3 = Me$



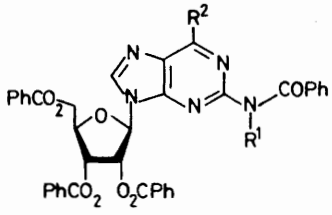
(2)



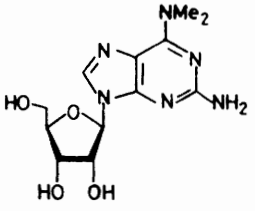
(3)



(4) a; R = H
b; R = Me



(5) a; $R^1 = H$, $R^2 = OSO_2Me$
b; $R^1 = Me$, $R^2 = OSO_2Me$
c; $R^1 = H$, $R^2 = NMe_2$



(6)

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† Satisfactory microanalytical and spectroscopic data have been obtained for all new crystalline compounds described.

‡ The *O*-benzoyl groups are removed within 12 h but the half-time for the removal of the *N*-benzoyl group with 33% $MeNH_2$–EtOH at 20 °C is *ca.* 24 h. This contrasts with a half-time of 200 min (see ref. 6) for the conversion of N^2-benzoylguanosine (**1**; $R^1 = R^2 = H$, R^3 = PhCO) into guanosine under the same conditions.

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