

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

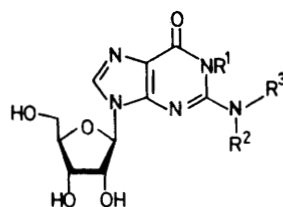
the protecting groups; (**5a**), which readily reacts with dimethylamine to give (**5c**), may be prepared from (**4a**) in good yield.

It is believed¹ 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*²*N*²-dimethyl-, and 7-methyl-guanosines [(1b), (1c), (1d), and (2), respectively]} found² in tRNA, only (1b) and (2) have been prepared directly³ by the methylation of guanosine (1a). *N*²-Methyl- and *N*²*N*²-dimethyl-guanosines (1c and 1d, respectively) have been prepared from 5-amino-1-β-D-ribofuranosyl-4-imidazolecarboxamide⁴ (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-methyl-guanosine (1c) by the direct methylation of a protected guanosine derivative.

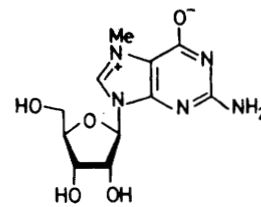
Reaction between *N*²*O*^{2'}*O*^{3'}*O*^{5'}-tetrabenzoylguanosine⁶ (4a) and an excess of methanesulphonyl chloride in the presence of triethylamine in dichloromethane solution gives its 6-*O*-mesyl derivative (5a), which may be isolated as a colourless crystalline compound, † m.p. 156–157 °C, in 75% 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-chloropurine⁷ 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; R¹ = Me, R² = 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-K₂CO₃ in water-dioxan (1:1 v/v) for 45 min at 20 °C. Fractionation of the products gives *N*²*O*^{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 (¹H n.m.r., u.v., and mass spectra; t.l.c. in several systems) to authentic material.

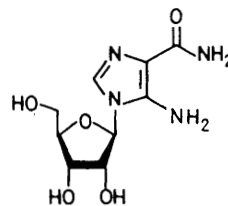
We are unaware of the previous use of an *O*-mesyl protecting group for base transformations in nucleoside or



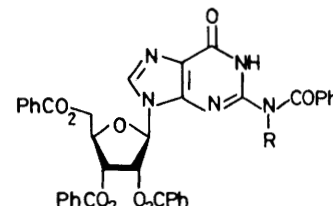
- (1) a; R¹ = R² = R³ = H
 b; R¹ = Me; R² = R³ = H
 c; R¹ = R² = H; R³ = Me
 d; R¹ = H; R² = R³ = Me



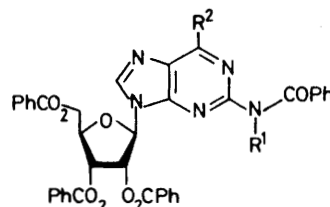
(2)



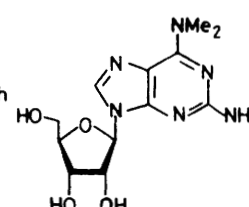
(3)



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



- (5) a; R¹ = H, R² = OSO₂Me
 b; R¹ = Me, R² = OSO₂Me
 c; R¹ = H, R² = NMe₂



(6)

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.

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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% MeNH₂-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; R¹ = R² = H, R³ = PhCO) into guanosine under the same conditions.

¹ R. H. Hall, 'The Modified Nucleosides in Nucleic Acids,' Columbia University Press, New York, 1971, pp. 295 *et seq.*

² B. G. Barrell and B. F. C. Clark, 'Handbook of Nucleic Acid Sequences,' Joynson-Bravvvers, Oxford, 1974.

³ A. D. Broom, L. B. Townsend, J. W. Jones, and R. K. Robins, *Biochemistry*, 1964, **3**, 494; J. A. Haines, C. B. Reese, and A. R. Todd, *J. Chem. Soc.*, 1962, 5281; J. W. Jones and R. K. Robins, *J. Amer. Chem. Soc.*, 1963, **85**, 193.

⁴ A. Yamazaki, I. Kumashiro, and T. Takenishi, *J. Org. Chem.*, 1967, **32**, 3032.

⁵ J. F. Gerster and R. K. Robins, *J. Amer. Chem. Soc.*, 1965, **87**, 3752; *J. Org. Chem.*, 1966, **31**, 3258.

⁶ C. B. Reese and R. Saffhill, *J.C.S. Perkin I*, 1972, 2937.

⁷ J. F. Gerster, J. W. Jones, and R. K. Robins, *J. Org. Chem.*, 1963, **28**, 945.