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SYNTHESIS OF O-6-ALKYLATED DEOXYGUANOSINE NUCLEOSIDES

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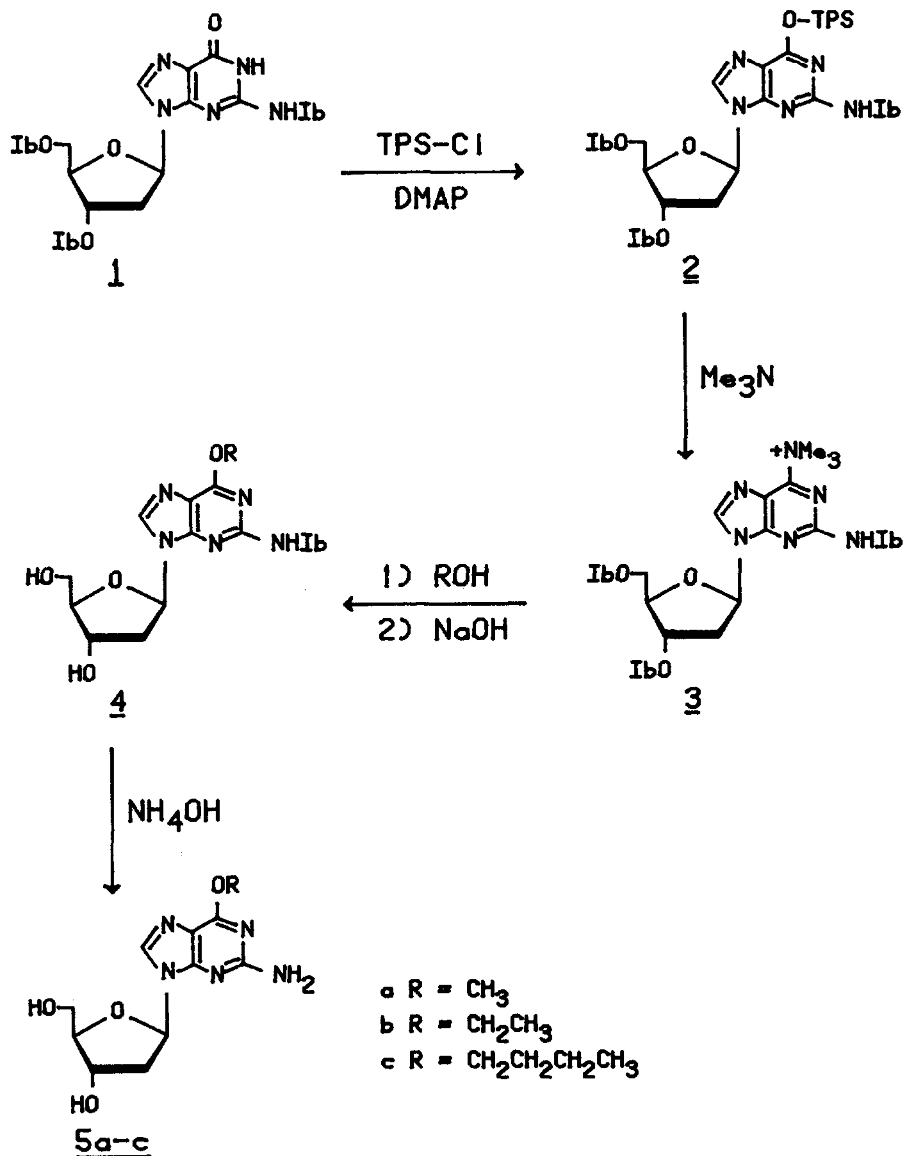
Abstract: A general route for synthesis of 6-O-alkyl-2'deoxyguanosine nucleosides is described. The key step is conversion of the 6-O-TPS derivative 2 to the 6-trimethylamino compound 3. The trimethylamino group is readily displaced by alcohols in the presence of DBU. Using this route the 6-O-methyl, ethyl and n-butyl 2'-deoxyguanosine derivatives 5a-c have been prepared in excellent overall yields.

The formation of 6-O-alkyl guanine derivatives in nucleic acids on exposure to alkylating agents is now well established as a potent mutagenic[1] and carcinogenic[2] modification. The base pairing properties of 6-O-methylguanine have been shown to resemble those of adenine, thereby miscoding for incorporation of uridine during transcription.[3,4] Further, while all alkylating agents give predominant N alkylation, the carcinogenicity of different types of alkylating agents appears to correlate with the extent of O-6 alkylation produced.[5] Thus while O-6 alkylation appears to be the more important modification, detailed study of such modified nucleic acid components has been severely limited by the accompanying N alkylation. Because of our interest in oligonucleotides which contain modified nucleosides such as 6-O-alkylguanine, and in more complete protection of the guanine residues during oligonucleotide synthesis,[6] we decided to develop a practical route to 6-O-alkylguanine nucleosides.

Since alkylation reactions are unsatisfactory, we looked instead to displacement of some O-6 derivative. A route to 6-O-alkyl ribonucleosides, through the corresponding 6-chloro derivatives, has been reported[7] and applied to deoxyguanosine.[4] Because of the acidic conditions employed, however, only a 15% yield is obtained for the chlorination reaction. Stabilization of the glycosidic linkage as reported by Robins for synthesis of the corresponding 6-chloro derivative from 2'-deoxyinosine[8] could probably be done with deoxyguanosine and would undoubtedly give better yields. Nevertheless, we chose to use guanosine



TPS = 2,4,6-triisopropylbenzenesulfonyl; DMAP = 4-dimethylaminopyridine; Ib = isobutyryl

6-O-sulfonyl derivatives which are readily prepared by the methods reported recently by Reese[9] and by Hata.[10] However, when we attempted direct reaction of 2 with methanol, under a variety of conditions, we obtained only trace amounts of 6-O-methyl products. The major product was always the parent guanosine derivative (1) apparently resulting from attack of methanol at sulfur, rather than at O-6.[11] To avoid this problem we took advantage of the extremely facile displacement of the sulfonate function by nitrogen nucleophiles,[9,10,12] in this case trimethylamine, to give a class of derivatives (e.g. 3) known to be susceptible to displacement by hard nucleophiles.[8,13] Reaction of 3 with excess alcohol in the presence of DBU gives the desired 6-O-alkyl derivative cleanly, within minutes.[14] Moreover, 3 is not isolated, and as it is also formed rapidly, conversion of the 6-O-sulfonate 2 to the 6-O-alkyl derivative is effected in about 30 minutes, as a one-flask procedure. Since some loss of the 3' and 5' isobutyryl groups invariably accompanies this sequence of reactions it is most convenient to remove the remaining hydroxyl isobutyryl groups immediately by treatment with 1N NaOH to give 4a-c in yields of 81% for 4a (mp 169-172°), 76% for 4b (mp 219-224°), and 90% for 4c (mp 101-105°) after purification by flash chromatography.[15]

The general procedure is to react triisobutyryldeoxyguanosine (1) with 2 eq of triisopropylbenzenesulfonyl chloride (TPS-Cl), 4 eq of triethylamine and 0.05 eq of 4-dimethylaminopyridine in CH_2Cl_2 solution at room temperature for two hours. The reaction mixture is immediately separated by flash chromatography[15] on silica to give 2 in 87% yield.[14] Conversion of 2 to 4a-c is effected in CH_2Cl_2 solution (1 ml/mmol) with 5-10 eq of the alcohol. Trimethylamine (1 ml/mmol) is added to this solution, at 0°, to give 3. After the reaction has been allowed to proceed for ten minutes 1.5 eq of DBU is added. Formation of the highly polar 3 and subsequent conversion to 4a-c are readily monitored by tlc. Displacement is generally complete within 20 minutes at 0°. The solution is then made 1N in NaOH and kept at 0° for ten minutes. Excess NH_4Cl is then added to neutralize the reaction and the product 4a-c is isolated by extraction with ethyl acetate. Ammonolysis of the N-isobutyryl group of 4a-c is exceptionally slow but is completed in 2-3 days at 50° to give 5a-c in quantitative yield.[14]

The procedure reported herein for "alkylation" represents a general route to a class of nucleoside derivatives which has always been largely inaccessible. We have already used it to prepare 6-O-alkyl protected deoxyguanosines of value for use in oligonucleotide synthesis[6] and have extended it to aryl derivatives. For example, 6-O-phenyldeoxyguanosine is also obtained in excellent yield.[16] Application to other nucleosides, using both alcohols and phenols, is under way. These results will be reported in detail shortly.

Acknowledgements

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References and Notes

1. P.F. Schendel and P.E. Robins, Proc. Natl. Acad. Sci. USA, 75, 6017-6020 (1978).
2. J. Cairns, Nature (London), 289, 353-357 (1981).
3. L.L. Gerchman and D.B. Ludlum, Biochimica et Biophysica Acta, 308, 310-316 (1973).
4. J.R. Mehta and D.B. Ludlum, Biochimica et Biophysica Acta, 521, 770-778 (1978).
5. B. Singer, Nature (London), 264, 333-339 (1976).
6. B.L. Gaffney and R.A. Jones, next paper in this issue.
7. J.F. Gerster, J.W. Jones, and R.K. Robins, J. Org. Chem., 28, 945 (1963).
8. M.J. Robins and G.L. Basom, Can. J. Chem., 51, 3161 (1973).
9. P.R. Bridson, W.J. Markiewicz and C.B. Reese, J.C.S. Chem. Comm., 447-448 and 791-792 (1977).
10. H.P. Daskalov, M. Sekine, and T. Hata, Tetrahedron Lett., 3899-3902 (1980).
11. While this work was in progress a report appeared [S.S. Jones, C.B. Reese, S. Sibanda, and A. Ubasawa, Tetrahedron Lett., 4755-4758, (1981)] in which displacement of a guanosine 6-O-methanesulfonyl group by phenols was reported. This result may be due to the "softer" nature of phenoxide vs. alkoxide.
12. C.B. Reese and A. Ubasawa, Tetrahedron Lett., 2265-2268 (1980).
13. J. Kiburis and J.H. Lister, J. Chem. Soc. (C), 3942-3947 (1971).
14. Satisfactory microanalytic and spectroscopic data have been obtained for all new compounds described.
15. W.C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 43, 2293-2295 (1978).
16. B.L. Gaffney and R.A. Jones, unpublished results.

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