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N^2-ISOBUTYRYL-O^6-[2-(*p*-NITROPHENYL)ETHYL]GUANINE: A NEW BUILDING BLOCK FOR THE EFFICIENT SYNTHESIS OF CARBOCYCLIC GUANOSINE ANALOGS

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Abstract

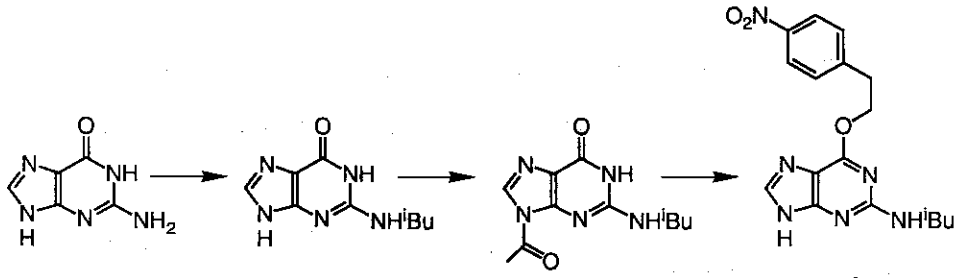
N^2-Isobutyryl-O^6-[2-(*p*-nitrophenyl)ethyl]guanine (**4**) allows the synthesis of different types of carbocyclic analogs of guanosine in high yield under Mitsunobu conditions. Only the desired N^9-substituted derivatives of guanine are formed.

The potential value of carbocyclic nucleoside analogs as antiviral agents has encouraged many research groups to address the challenges inherent in their synthesis[3,4,5,6]. Especially problematic is the preparation of purine analogs, in particular those bearing the guanosine nucleus. While pyrimidine analogs of nucleosides might be synthesised by stepwise construction of the heterocyclic ring around a carbocyclic amine[7,8,9], the same strategy for the construction of purine ring systems involves long reaction sequences[10,11,12,13]. Further, attachment of cyclopentane or other substituents to a purine via direct alkylation often yields both N^7 and N^9 substituted derivatives[14] which are often difficult to separate. Alkylation of purines using epoxides has been successfully applied to the preparation of carbocyclic analogs of nucleosides[15,16,17,18,19]. However, this approach yields ring systems that are hydroxylated at an inconvenient position[20].

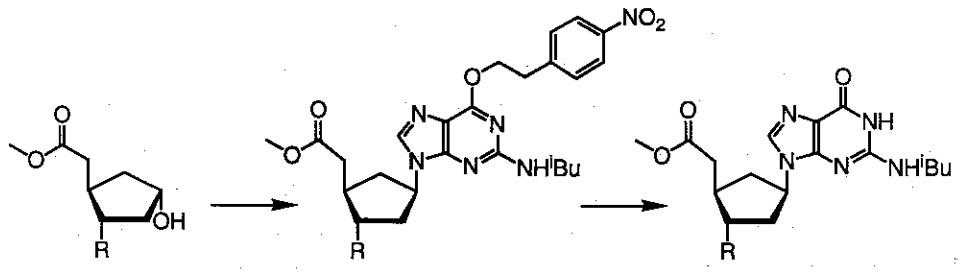
Recent efforts from this laboratory have been directed towards preparing analogs of oligonucleotides having dimethylene sulfide, sulfoxide, and sulfone units replacing the phosphate backbone as potential antisense reagents[21,22]. As a part of this work, we wished to have a variant of these analogs where the ring oxygen is substituted by a $-CH_2-$ group. The preparation of derivatives of guanosine proved to be especially problematic. Reports that 6-chloropurine could replace a primary hydroxyl group under Mitsunobu conditions[23] and success in our laboratories[24] and elsewhere[25] developing Mitsunobu-type conditions for introducing nucleoside bases by replacing a secondary hydroxyl group in carbocyclic systems encouraged us to search for a derivative of guanine that might be

easily introduced in different carbocyclic hydroxy compounds using Mitsunobu-type conditions without forming mixtures of N^7- and N^9-isomers.

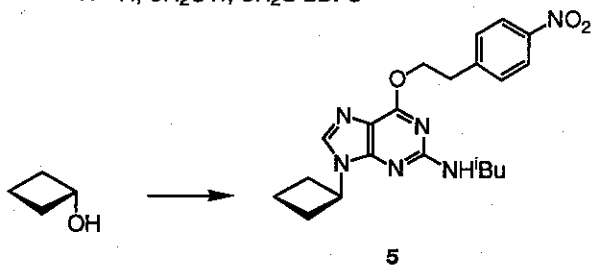
Among the different guanine derivatives and precursors tested, N^2-isobutyryl-O^6-[2-(*p*-nitrophenyl)ethyl]guanine (**4**) yielded by far the most successful results. The guanine nucleophile **4** was available readily and in large scale from guanine (**1**) via intermediates **2** and **3**[26] in an overall yield of 63%.



Compound **4** could be introduced in a wide variety of different cyclopentanol cores in yields between 70 and 75%, and the corresponding N^2-protected carbocyclic guanosine analogs were obtained by treatment of the intermediate with DBU in pyridine[27] in overall yields between 65 and 70%[28].



R = H, CH_2OTr, CH_2O^tBDPS



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Derivative **4** appears to be the most useful reagent available for synthesizing carbocyclic guanosine analogs. To illustrate its versatility, **4** was used to prepare the strained cyclobutane derivative **5** in 53% yield.

EXPERIMENTAL SECTION

N^2-Isobutyrylguanine-monohydrate (**2**): Following a procedure analogous to that used to prepare N^2-acetylguanine [29], isobutyric acid anhydride (21.36 g, 135 mmol) was added at room temperature to a suspension of guanine (**1**, 7.56 g, 50 mmol) in N,N-dimethyl-acetamide (100 ml). The reaction mixture was heated at 150°C for 2 hours, cooled to room temperature and evaporated under reduced pressure to 1/10 of its volume. The precipitated crude product was collected and crystallised from boiling ethanol/water (1:1, 1500 ml) to yield **2** (10.03 g, 84%) as colorless crystals.

9-Acetyl-N^2-isobutyryl-guanine (**3**): A suspension of **2** (14.36 g, 60 mmol) in DMF (75 ml) and acetic acid anhydride (15 ml, 158 mmol) was stirred at 100°C until a clear solution was obtained (30 min). Solvent was completely removed by evaporation under reduced pressure, and the residue suspended in EtOH (30 ml). Filtration and drying yielded **3** (14.10 g, 89%) as colorless crystals .

N^2-isobutyryl-O^6-[2-(p-nitrophenyl)ethyl]guanine (**4**): A suspension of **3** (5.26 g, 20 mmol), triphenylphosphine (8.89 g, 30 mmol) and 2-(*p*-nitrophenyl)ethanol (5.05 g, 30 mmol) in dioxane (200 ml) was treated within 30 min with diethyldiazodicarboxylate (DEAD, 95%, 5.0 ml, 30 mmol). The mixture was stirred at room temperature overnight. After evaporation of the solvent, the residue was taken up in EtOH (1300 ml) and water (1300 ml) and the mixture heated under reflux for 30 min. The clear solution was then cooled to room temperature, to 0°C, and then to -18°C in stages over a period of 16 h, yielding crystals of **4** as flakes. Filtration and drying yielded **4** (6.22 g, 84%) which was slightly contaminated with triphenylphosphine oxide. This product could be used directly for the syntheses of carbocyclic guanosine analogs. An analytically pure sample was obtained by recrystallisation from chloroform/methanol (1:1)[30].

Mitsunobu reaction: In a typical experiment, very finely powdered **4** (370 mg, 1 mmol) was suspended in dry dioxane (15 ml) and heated at reflux for 30 min. The suspension was then cooled to room temperature and treated with triphenylphosphine (350 mg, 1.33 mmol) and the appropriate cyclic alcohol (0.63 mmol) in dry THF (10 ml). Diethyl-diazodicarboxylate (DEAD, 95%, 0.22 ml, 1.33 mmol) was added over 30 min and the suspension was stirred overnight to yield a clear solution. The reaction mixture was adsorbed onto 4.5 g silica gel and rapidly chromatographed on silica gel (140 g, eluted with dichloromethane/methanol). Products that were especially polar were often contaminated at this point with triphenylphosphine oxide. This was removed in these derivatives following deprotection of the guanine derivative.

Removal of the p-nitrophenylethylgroup: The carbocyclic nucleoside intermediate (1 mmol) from the Mitsunobu reaction, either pure or contaminated with triphenylphosphine oxide, was dissolved in dry pyridine (20 ml) and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.3 ml, 2 mmol). The mixture was stirred overnight at room temperature. The crude reaction mixture was adsorbed onto silica gel (4 g) and chromatographed on silica gel (100 g, eluted with CH_2Cl_2/MeOH) to yield the final N^2-isobutyrylguanine derivative.

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30 mp: >260°C dec. IR (KBr): 3310, 3110, 2970, 1685, 1620, 1590, 1520, 1435, 1410, 1350, 1260, 1220, 1140, 1105, 970, 930, 860, 790, 645. ^{1}H-NMR (DMSO-d_6): 1.10 (d, J= 6.8, 6H, ^{i}Bu-CH_3); 2.86 (qq=sept., J=6.8, 1H, sec ^{i}Bu-H); 3.32 (t, J= 6.8, 2H, CH_2-Ph); 3.00-3.80 (s, br., 1H, H-N^9); 4.78 (t, J= 6.8, CH_2-O); 7.65-7.69 (m, 2 arom. H); 8.16-8.20 (m, 2 arom. H); 10.25 (s, br., NH-CO). MS: 370 (M^+, 7), 300 (17), 221 (38), 152 (26), 151 (100), 150 (11), 149 (67), 134 (11), 119 (29), 110 (14), 109 (14), 103 (38), 102 (17), 91 (32), 77 (72), 71 (14), 65 (11), 63 (11), 55 (10), 53 (13), 51 (28), 50 (15), 43 (85), 41 (26). Anal. calcd for $C_{17}H_{18}N_6O_4$ (370,4): C 55.13, H 4.90, N 22.69, O 17.28; found C 54.83, H 4.72, N 22.37.

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