Reaction of 3',5'-Di-*O*-acetyl-2'-deoxyinosine with the Chlorinating Agent PPh_3–CCl_4: Synthesis of the 6-chloroderivative and of a new base linked dimer, useful intermediate to ^{15}N-1-labelled 2'-deoxyinosine

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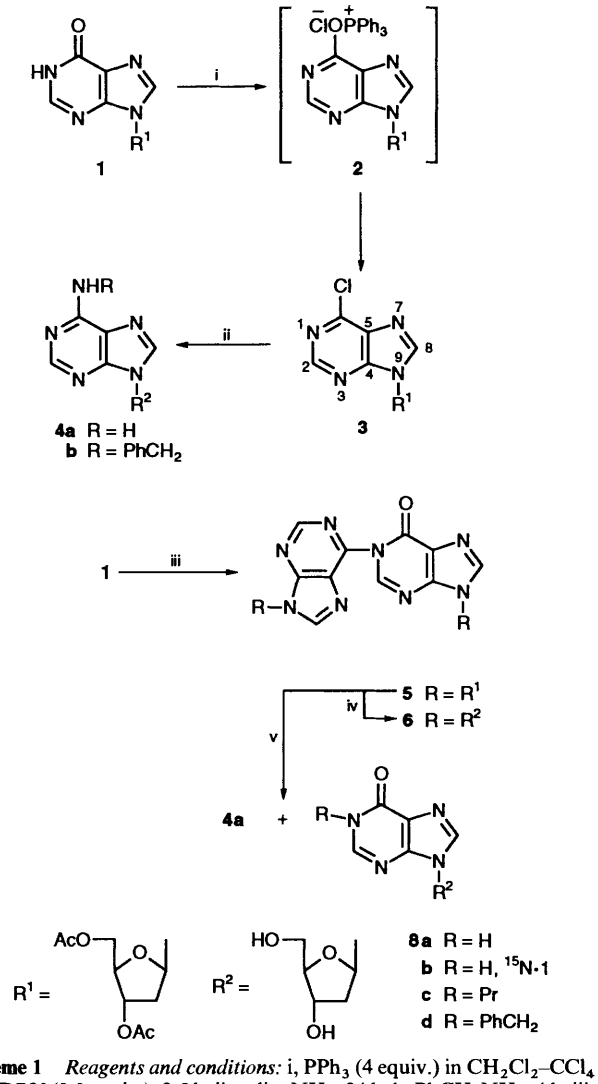
Treatment of 3',5'-di-*O*-acetyl-2'-deoxyinosine **1** with PPh_3–CCl_4 in the presence of catalytic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded 6-chloro-9-(2'-deoxy-3',5'-di-*O*-acetyl-β-D-ribofuranosyl)purine **3**. Use of an excess of DBU gave the new dimeric bipurine **5** (90%) which proved to be a useful intermediate for obtaining, in one step, [^{15}N-1]-2'-deoxyinosine.

Many 6-substituted purine nucleosides have been prepared and their biological activities evaluated.[1] A key synthetic intermediate in such work is a purine nucleoside with a good leaving group in the C-6 position. That most commonly used, *i.e.* the 6-chloropurine nucleoside, is prepared either by coupling between the activated sugar and the chlorinated base[2] or, more conveniently, by direct chlorination of the nucleoside. Use of reagents such as $POCl_3$[3] and $SOCl_2$[4] on 2'-deoxypurine nucleosides was unsuccessful owing to the lability of the glycosidic bond under the acidic conditions of the reactions. For 2'-deoxyinosine, direct base chlorination with $SOCl_2$–DMF[5] in CH_2Cl_2 was only successful when two powerful electron-withdrawing groups had been introduced on the sugar thus rendering the *N*-glycosidic bond less acid-labile. Such drawbacks led us to try milder chlorinating methods.

Recently, we reported[6] that the adduct PPh_3–CCl_4 chlorinates the C-4 position of thymine nucleosides under non-acidic conditions to afford high product yields, even with 2',3'-dideoxynucleosides, which are known to have a very acid-sensitive *N*-glycosidic bond. Here we describe the reaction of this reagent with 3',5'-di-*O*-acetyl-2'-deoxyinosine **1**.

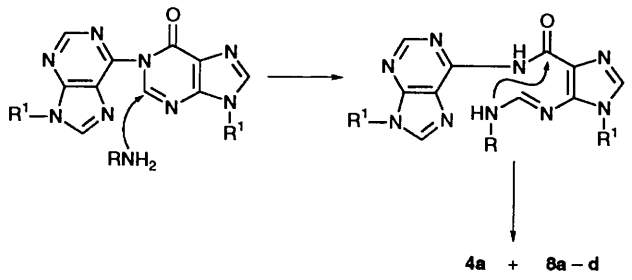
Compound **1** (1 mmol) when treated under reflux with PPh_3 (2 mmol) in CCl_4–CH_2Cl_2 for 6 h gave only traces of the 6-chloro derivative **3**; however, in the presence of DBU (0.3 mmol) the product yield rose to 40%. It seems likely that DBU acts as an acceptor of the N-1 proton of the base, thus increasing the nucleophilicity of O-6 function towards the adduct $[Ph_3P\text{-}CCl_3]^+Cl^-$. The structure of **3** was confirmed on the basis of spectroscopic evidence and by conversion[5] of the compound into 2'-deoxyadenosine **4a** and N(6)-benzyl-2'-deoxyadenosine **4b** upon treatment with liq. NH_3 and benzylamine, respectively (Scheme 1). An attempt to further increase the yield of **3** by increasing the amount of DBU used gave, unexpectedly, product **5** (90%). Formation of **5** is thought to arise as a consequence of nucleophilic attack of the negatively charged N-1 of **1** on the C-6 of the O(6)-triphenylphosphonium intermediate **2**. The possibility of **3** being a transient reactive intermediate in the dimer formation was excluded since it is stable towards nucleophilic displacement with **1** under the same reaction conditions.

The reactivity of **5** towards the nucleophiles aqueous ammonia, propylamine and benzylamine was then examined. In the last two aminolysis afforded, in a 1:1 ratio, **4a** and the corresponding N(1)-alkylinosine derivative **8c**, **d**, identified on the basis of spectral evidence and by comparison with authentic samples independently synthesized by a reported procedure.[7] With ammonia **5** yielded **4a** and 2'-deoxyinosine **8a** (1:1, 85%). The mechanism proposed for these reactions assumes an initial nucleophilic attack of the amine at C-2 of the hypoxanthin-1-yl



Scheme 1 *Reagents and conditions:* i, PPh_3 (4 equiv.) in CH_2Cl_2–CCl_4 and DBU (0.3 equiv.), 2.5 h; ii, a: liq. NH_3, 24 h, b: $PhCH_2NH_2$, 4 h; iii, PPh_3 (2 equiv.) in CH_2Cl_2–CCl_4 and DBU (3.5 equiv.) 40 min; iv, Et_3N (19 equiv.) in MeOH, 5 h; v, a: aq. NH_3 (32%), b: aq. $^{15}NH_3$ (3.3 N), c: $PrNH_2$ (18 equiv.) 15 h, d: $PhCH_2NH_2$ (10 equiv.) 15 h

base with a subsequent cleavage of its N(1)–C(2) bond, followed by a ring closure with the concomitant loss of a 2'-deoxyadenosine unit (Scheme 2). Such a proposal is in agreement with the known reactivity of C-2 towards the nucleophiles in N(1)-alkyladenine derivatives[7,8] and with the



Scheme 2

results for the reactivity of N(1)-aminopurine salts with amines.[9] Support for the proposed mechanism was obtained when treatment of **5** with [^{15}N] ammonia gave 2'-deoxyadenosine **4a** and 2'-deoxy[^{15}N-1]inosine **8b**, products identified on the basis of spectroscopic evidence (heterocoupling ^{1}H and ^{13}C NMR experiments). By this route, 2'-deoxy[^{15}N-1]-inosine (**8b**, 38% overall yield), starting from **1**, was obtained in only two steps.

Compound **5**, which was unreactive to nucleophilic attack by alcohols (60 °C), when treated in methanol with Et_3N at 50 °C for 5 h afforded the deacetylated compound **6** (78%).

In conclusion, the adduct PPh_3–CCl_4 in the presence of DBU was shown to be a convenient reagent for chlorinating the C-6 position of a purinyl-6-one nucleoside under very mild conditions. In addition, a new dimeric nucleoside with N(1)–C(6) linked bases was obtained, which proved useful for the easy introduction of a ^{15}N atom into a purine ring; this is a more efficient procedure than that involving a Dimroth rearrangement.[10]

Experimental

General Procedures.—TLC plates (Merck, silica gel 60, F254) were developed in solvent systems: A [chloroform–ethyl-acetate (6:4, v/v)], B [chloroform–methanol (9:1, v/v)] and C [chloroform–methanol (7:3, v/v)]. PPh_3 was dried under reduced pressure at 50 °C for 15 h. CH_2Cl_2 and CCl_4 were dried by treatment with P_2O_5 and were then distilled.

^{1}H and ^{13}C NMR results for the compounds described are available as a Supplementary publication [Sup. No. 57008 (6 pp.)]*.

6-Chloro-9-(2'-deoxy-3',5'-di-O-acetyl-β-D-ribofuranosyl)-purine **3**.—3',5'-Di-*O*-acetyl-2'-deoxyinosine **1** (336 mg, 1 mmol) and triphenylphosphine (524 mg, 2 mmol) were suspended in CH_2Cl_2–CCl_4 [1:1.4 (v/v); 12 cm^3] and the resulting mixture was stirred and kept at reflux for 30 min, DBU (15 mm^3, ca. 0.1 mmol) was then added to the mixture followed by two further portions of PPh_3 (262 mg, 1 mmol each), dissolved in CCl_4 (1 cm^3) and of DBU (15 mm^3, 0.1 mmol each) introduced over the next 2 h. After this, the mixture was cooled, dried, concentrated under reduced pressure and purified on a silica gel column eluting with increasing amounts of ethyl acetate in chloroform (from 50 to 60%) to afford pure **3** (140 mg, 40%); R_F 0.3 system A; $[\alpha]_D$ −5.5 ($CHCl_3$, *c* 0.2); λ_{max}/nm ($CHCl_3$) 263 (6900); *m/z* (FAB) 355 (MH^+, ^{35}Cl), 201 and 155.

1-[9-(2'-Deoxy-3',5'-di-O-acetyl-β-D-ribofuranosyl)purin-6-yl]-3',5'-di-O-acetyl-2'-deoxyinosine **5**.—A stirred mixture of **1** (336 mg, 1 mmol) and triphenylphosphine (524 mg, 2 mmol) in CH_2Cl_2–CCl_4 [1:1, (v/v); 12 cm^3] was treated with DBU (400 mm^3, 2.7 mmol) under reflux for 20 min after which further DBU (125 mm^3, 0.84 mmol) was added to it. The mixture was heated under reflux for a further 20 min, after which it was cooled, concentrated under reduced pressure and purified on a silica gel column eluting with $CHCl_3$–MeOH (96:4, v/v) to give pure **5** (590 mg, 90%); R_F 0.5 system B; $[\alpha]_D$ −24 ($CHCl_3$, *c* 0.16); λ_{max}($CHCl_3$)/nm 252 (12 500) and 265 (13 000); *m/z* (FAB) 655 (MH^+), 454 and 255.

1-[9-(2-Deoxy-β-D-ribofuranosyl)purin-6-yl]-2'deoxyinosine **6**.—Triethylamine (1 cm^3, 7.2 mmol) was added to a stirred solution of **5** (250 mg, 0.38 mmol) in MeOH (3 cm^3). After 5 h at 50 °C the mixture was concentrated and purified on a silica gel column eluting with increasing amounts of MeOH in $CHCl_3$ (from 10 to 25%), to give pure **6** (144 mg, 78% yield); R_F 0.35 system C; $[\alpha]_D$ −12.8 (MeOH, *c* 0.08); λ_{max}(MeOH)/nm 254 (12 000) and 265 (13 000); *m/z* (FAB) 487 (MH^+) and 370.

Reaction of **5** *with Aq.* $^{15}NH_3$.—**5** (65 mg, 0.1 mmol) was treated with aq. $^{15}NH_3$ (3.3 N) [(99% ^{15}N), 4 cm^3] at 50 °C for 7 h. The mixture was dried, concentrated under reduced pressure and purified on two silica gel plates (20 × 20 cm, 0.5 mm, Merck), developed in the eluent system C. The bands at R_F 0.4 and 0.5, scratched from the plates and eluted with $CHCl_3$–MeOH (1:1, v/v), afforded 2'-deoxyadenosine **4a** (22 mg) identified by comparison with an authentic sample, and 2'-deoxy[^{15}N-1]inosine **8b** (22 mg).

Reaction of **5** *with Amines; Products* **8c, d**.—Compound **5** (196 mg, 0.3 mmol) was treated with propylamine (1.5 cm^3, 18 mmol) at 50 °C for 15 h after which it was dried, concentrated under reduced pressure and purified on a silica gel column eluting with increasing amounts of MeOH in $CHCl_3$ (from 10 to 30%) to give **4a** (64 mg) and **8c** (72 mg) (1:1, 81%).

Analogously the reaction of **5** (196 mg, 0.3 mmol) with benzylamine (1.0 cm^3, 9.7 mmol), after purification performed on silica gel column as for **8c**, afforded **4a** (66 mg) and **8d** (87 mg), *ca.* 1:1 (84% yield).

8c: R_F 0.5 system C; $[\alpha]_D$ −13.6 (MeOH, *c* 0.09); λ_{max}(MeOH)/nm 252 (6800); *m/z* (FAB) 295 (MH^+).

8d: R_F 0.55 system C; $[\alpha]_D$ −7.9 (MeOH, *c* 0.11); λ_{max}/nm 252 (7300); *m/z* (FAB) 343 (MH^+).

Acknowledgements

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