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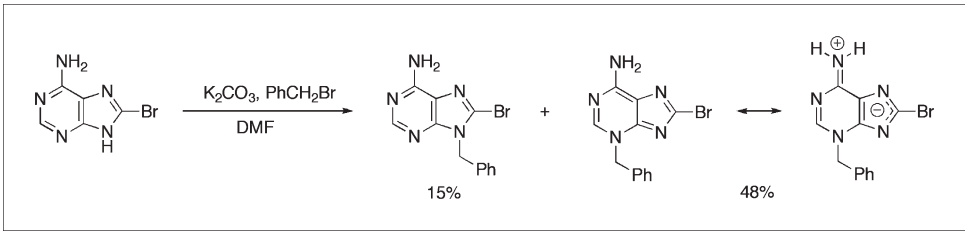

8-Bromoadenine was benzylated in the presence of base to give a mixture of two regioisomers. One was easily recognized as 9-benzyl-8-bromoadenine, but the other structure could not be determined with absolute certainty by NMR. Therefore, X-ray crystallography was used to prove that the benzyl group was attached to N-3. Furthermore, it is shown that the 3-benzyl adenine derivative exists as the amine tautomer both in the crystalline state as well as in solution (DMSO-d_6), with restricted rotation around the N^6—C6 bond.

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INTRODUCTION

Generally, reaction of adenine with alkyl halides under neutral conditions gives the 3-alkylated product as the major isomer. However, selective N-9 alkylation is often seen when the reaction is performed in the presence of a base [1]. The numbering of the adenine system is shown in Figure 1. When 8-bromoadenine is alkylated under basic conditions, the selectivity for the 9-position is generally reduced, and mixtures of the 3- and 9-alkylated isomers are often reported [2–6]. The isomeric distribution is qualitatively the same in Cu-mediated N-arylation of 8-bromoadenine [7]. When 8-bromoadenine was benzylated in our laboratories under basic conditions, we also obtained two isomers, but we found that the position of the benzyl group in one of the isomers could not be determined with absolute certainty by NMR spectroscopy. Furthermore, the ^{1}H-NMR spectrum of the same compound showed some intriguing features (discussed below) and, as a result, we performed thorough NMR and X-ray structural studies on this compound.

RESULTS AND DISCUSSION

8-Bromoadenine (**1**) [2] was reacted with benzyl bromide in the presence of K_2CO_2 at ambient temperature as shown in Scheme 1. The minor product was easily identified as the 9-benzylated isomer **2** based on comparison with data reported before [4] as well as ^{1}H-^{13}C HMQC and HMBC NMR experiments. Compound **2** is reported to be the major isomer when the benzylation was performed at higher temperature [4], but in our hands more than two products were formed at elevated temperatures and the purification of products was rather tedious. The spectral data for our major product were in good agreement with what has been reported for compound **3** before. However, despite the fact previous literature structure elucidation is claimed to be based on ^{1}H-^{13}C HMQC and HMBC NMR (no details given) [4], we found our HMBC data to be inconclusive. The CH_2 protons correlate to two carbon shifts; the C-2 at 143.9 ppm and a peak at 149.8 ppm (quaternary C). Unfortunately, it was not possible to determine if the latter peak was the C-4 or C-6 shift, and hence, it was not possible to establish if the benzyl group was situated at N-3 or N-1. Both the peak at 149.9 ppm and a second peak (quaternary C) at 153.6 ppm correlated to H-2 and neither of them correlated with the NH_2 in the HMBC spectrum.

Because there are several reports on the formation of N-3 alkylated 8-bromoadenine, where the structure elucidation is reported to be based on ^{1}H-^{13}C HMQC and HMBC NMR [4,5,7], which in fact may not be conclusive, we decided to determine with absolute certainty whether the major product formed was the isomer **3** or **4**. For these purposes, we turned to X-ray crystallography. Before this investigation, crystal structures of ten 8-bromoadenines were available in the Cambridge Structural Database (CSD, Version 5.31 of November 2009 [8]). All these molecules carry an additional ethyl group or a sugar moiety, which is always attached to N-9 as for isomer **2**.

The result of the X-ray structural investigation shown in Figure 1 confirms that isomer **3** has been crystallized. This is not only the first ever X-ray structure of an N-3 functionalized 8-bromoadenine but in fact also the first N-3 functionalized adenine where neither N-7 nor N-9 act as ligands for metal ions or carry additional

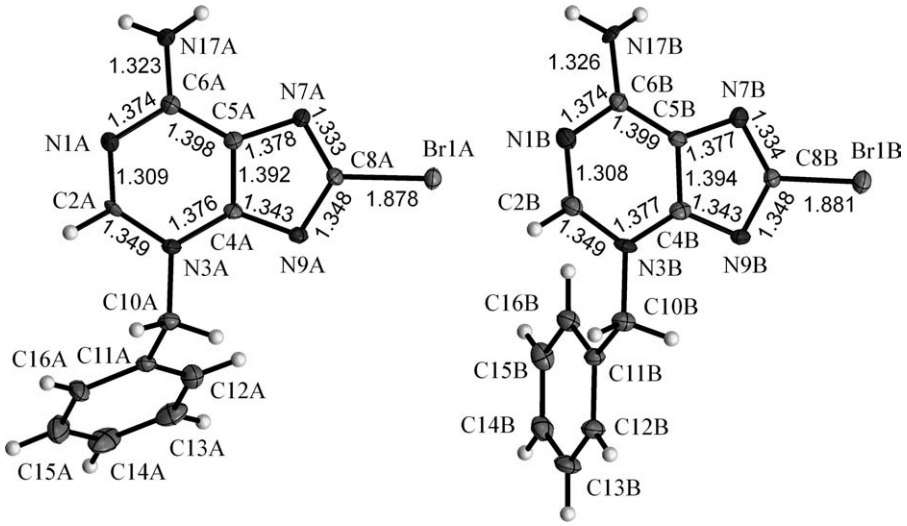


Figure 1. The two adenine molecules in the asymmetric unit of **3** with atomic numbering indicated (not in correct crystallographic positions relative to each other). Displacement ellipsoids are drawn at the 50% probability level, H atoms are spheres of arbitrary size. Important bond lengths (in Å) have been indicated, estimated standard deviations are 0.005–0.006 Å. The different orientations of the benzyl groups are defined by the torsion angles C2A—N3A—C10A—C11A = 70.6(6)°, N3A—C10A—C11A—C12A = 76.7(6)°, C2B—N3B—C10B—C11B = 90.8(6)°, and N3B—C10B—C11B—C12B = 177.7(5)°.

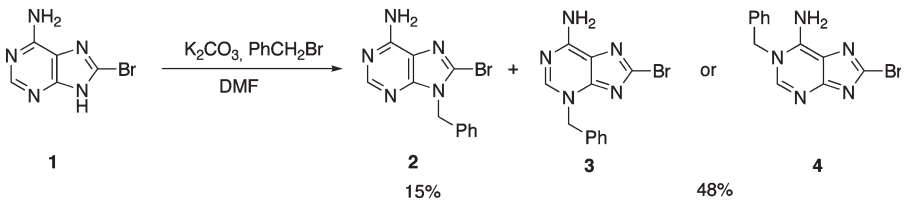
functional groups. Bond lengths and bond angles are roughly the same for the two molecules in the asymmetric unit and correspond to the regular amino tautomer. Both amino H-atoms were easily located in the electron density map and participate in strong hydrogen bonds as shown in Figure 2.

In the ^{1}H-NMR spectrum of compound **3** in DMSO-d_6 solution, there are two distinct NH signals (8.07 and 8.23 ppm), in contrast to the spectrum of the 9-benzylated product **2**, where one broad singlet for the NH_2-group is seen. Two NH signals have also been observed in spectra of other 3-alkylated adenines [3–6], but this phenomenon has only been discussed once previously and the hypothesis presented was that the compound studied must exist in solution as an imine tautomer. However, no experimental evidence is given [6]. We thought that the reason for the splitting of the NH signals could either be that compound **3** exists as an imine tautomer in solution **3b** or **3c** (Fig. 3) or that there is restricted rotation around the N^6—C6 bond leading to two resonances for the NH_a and NH_b. This could be the case if resonance forms **3a′** and or **3a″** contribute to the structure of **3a** (Fig. 4). Computational calculations have indicated that the amino tautomer of 3-methyladenine is more stable than any of the possible imine forms in the gas phase [9], and these calculations support the hypothesis shown in Figure 4.

^{1}H-^{15}N HSQC NMR spectroscopy showed that both NH signals correlated to the same nitrogen signal at 125.7 ppm (relative to $^{15}NH_3$) proving that compound **3** exists as the amino tautomer **3a** in solution (DMSO-d_6). It is interesting to note that the NH_2 in compound **3** is shifted substantially downfield compared with for instance the NH_2 in 9-methyladenine which resonances at 79.6 ppm (−300.9 ppm relative to $Me^{15}NO_2$) [10] indicating more sp_2 character for the N^6 in compound **3a**. The coalescence temperature for the NH_a and NH_b was not determined, but at 65°C only one broad signal from the NH_2 could be seen in the ^{1}H-NMR spectrum.

In summary, we have shown with absolute certainty that benzylation of 8-bromoadenine in the presence of K_2CO_3 gives a mixture of the N-3 and the N-9 alkylated isomers, with the former as the major product. The N-3

Scheme 1



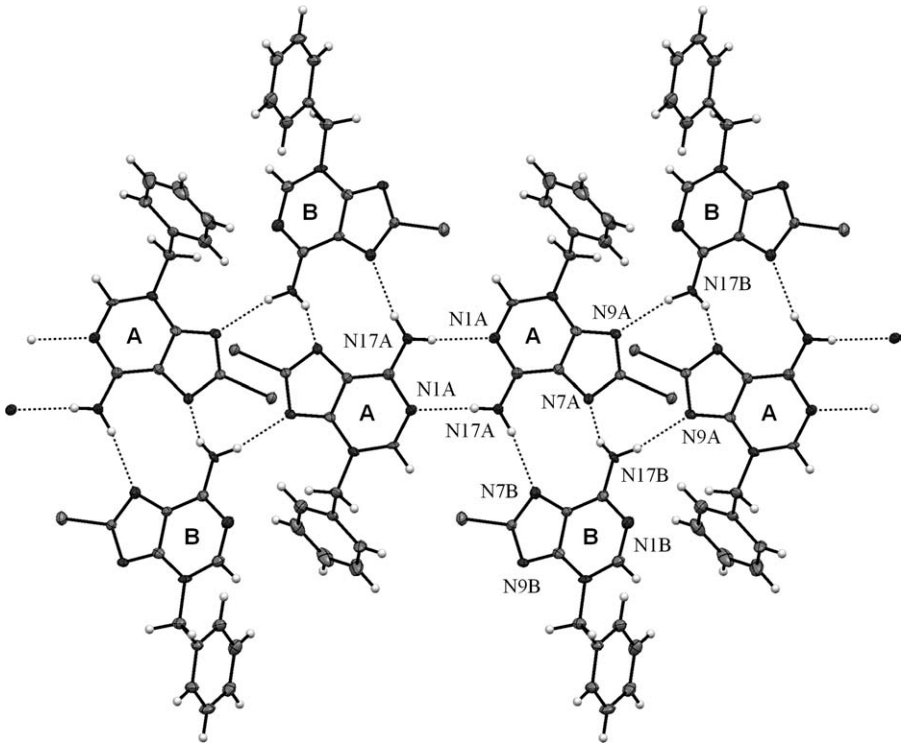


Figure 2. Adenine molecules connected by hydrogen bonds into one-dimensional chains or tapes. The indicated H···N distances are in the range 2.09(4) – 2.16(3) Å. It can be seen that molecule **A** participates in a larger number of strong interactions as the aromatic N atoms accept a total of three H atoms compared with only one H atom for molecule **B**.

selectivity is higher when the reaction is conducted at ambient temperature compared with elevated temperatures. Furthermore, it is shown that the 3-benzyl adenine derivative exists as the amine tautomer both in the crystalline state as well as in solution (DMSO-d_6), but with restricted rotation around the N^6—C6 bond.

EXPERIMENTAL

The ^{1}H-NMR spectra were recorded at 300 MHz with a Bruker Avance DPX 300 instrument and the decoupled ^{13}C-NMR spectra were recorded at 75 MHz using the instrument mentioned above. The ^{1}H-^{15}N HSQC spectrum was recorded with a Bruker AVII 600 instrument (pulse program hsqcetf3gpsi, using sensitivity improvement). All NMR spectra were obtained in DMSO-d_6. Mass spectra under electron impact conditions were recorded with a VG Prospec instrument at 70 eV ionizing voltage, and are presented as *m/z* (% relative intensity). Melting points were determined with a Büchi Melting Point B-545 apparatus and are uncorrected. DMF was obtained from a solvent purification system, MB SPS-800 from MBraun. Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 09385). All other reagents were commercially available and used as received.

9-Benzyl-8-bromo-9H-purin-6-amine (2) and 3-benzyl-8-bromo-3H-purin-6-amine (3). A mixture of 8-bromoadenine [2] (220 mg, 1.03 mmol), DMF (5 mL) and potassium carbonate (280 mg, 2.03 mmol) was stirred at ambient temperature under N_2 atmosphere for 30 min. Benzyl bromide (0.18 mL, 1.5 mmol) was added and the mixture stirred for another 4 h. The mixture was filtered and the solvent evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 0–5% MeOH in CH_2Cl_2 to give compounds **2** (45 mg, 15%) and **3** (128 mg, 42%).

9-Benzyl-8-bromo-9H-purin-6-amine (2). Colorless powdery crystals, m.p. 238°C (Lit. [4], 226–227°C). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.16 (s, 1H, H-2), 7.47 (br s, 2H, NH_2),

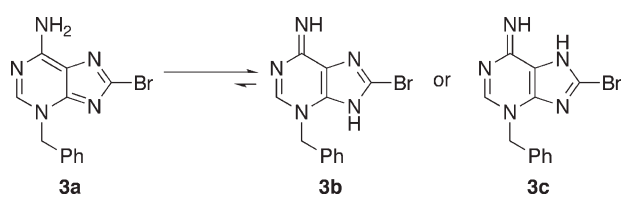


Figure 3. Possible tautomers of compound **3** in solution.

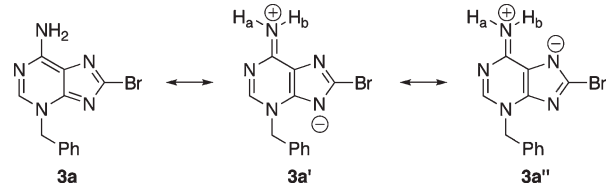


Figure 4. Resonance forms **3a**′ and or **3a**″ that may contribute to the structure of tautomer **3a**.

7.33–7.21 (m, 5H, Ph), 5.35 (s, 2H, CH_2); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 154.7 (C-6), 153.0 (C-2), 150.9 (C-4), 135.9 (C-8), 128.7 (Ph), 127.8 (Ph), 127.1 (Ph), 126.5 (Ph), 119.0 (C-5), 46.6 (CH_2); ms: *m*/*z* 305/303 (26/26, M^+), 91 (100).

3-Benzyl-8-bromo-3H-purin-6-amine (3). Colorless powdery crystals, m.p. 233–235°C (Lit. [4], 239–240.5°C). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.53 (s, 1H, H-2), 8.22 (br s, 1H, NH_2), 8.10 (br s, 1H, NH_2), 7.40–7.29 (m, 5H, Ph), 5.46 (s, 2H, CH_2); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 153.6 (C-6), 149.8 (C-4), 144.0 (C-2), 139.3 (C-8), 135.8 (Ph), 128.7 (Ph), 128.1 (Ph), 127.8 (Ph), 121.5 (C-5), 52.0 (CH_2); ms: *m*/*z* 305/303 (28/28, M^+), 91 (100).

X-ray crystallographic analysis for compound 3. Crystals of **3** suitable for X-ray crystallography were obtained from a solution of compound **3** in acetonitrile placed inside a larger vial containing ethyl acetate. They were unstable at room temperature due to loss of co-crystallized ethyl acetate solvent molecules, and X-ray data collection with Apex-2 [11] was thus performed at 105 K. Apex II single crystal CCD-diffractometer, MoK_α radiation ($\lambda = 0.71069$ Å), 0.30 mm × 0.30 mm × 0.26 mm block-shaped specimen, data integration and cell refinement with SAINT-Plus [12], absorption correction by SADABS [13], structure solution by and least-squares refinement on F^2 with SHELXTL [14]. Solvent molecules are located on two different inversion centers, each with a maximum allowed occupancy of 0.500 and form distinct channels running through the crystal along the *ab*-diagonal. The geometries of independent solvent molecules were constrained to be similar within a standard deviation of 0.002 Å for bond lengths and 0.003 Å for 1–3 distances.

3-Benzyl-8-bromo-3*H*-purin-6-amine ethyl acetate solvate: $C_{12}H_{10}BrN_5 \cdot 0.5C_4H_8O_2$, M = 348.21, triclinic, $P\bar{1}$, $a = 8.4937(6)$ Å, $b = 12.9096(9)$ Å, $c = 15.2238(10)$ Å, $\alpha = 101.723(1)°$, $\beta = 105.162(1)°$, $\gamma = 108.192(1)°$, $Z = 4$, $N_{observed} = 5830$, $R[F^2 > 2\sigma(F^2)] = 0.058$, $wR(F^2) = 0.146$, CCDC 786213.

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