SYNTHESIS OF ADENINE 7-OXIDE FROM ADENINE: UTILIZATION OF A BENZYL GROUP AS A CONTROL SYNTHON AT THE 3-POSITION

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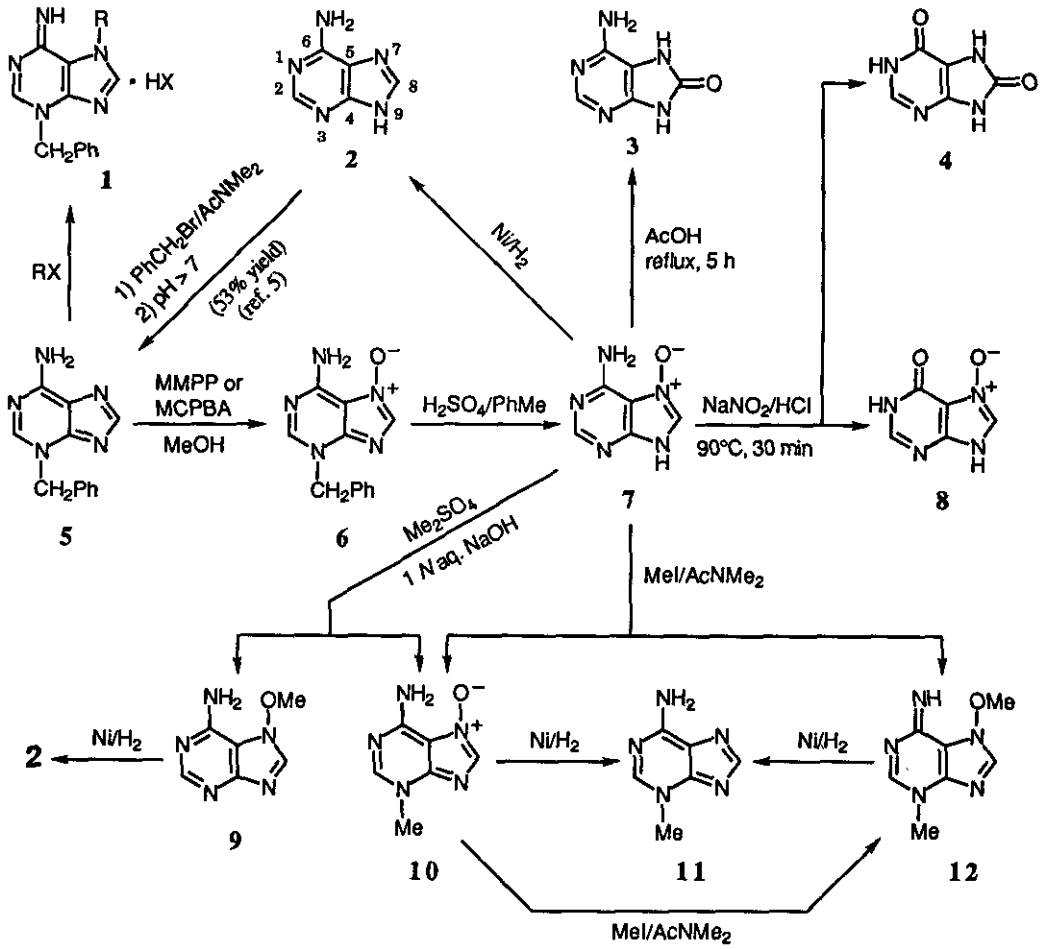
Abstract——The first unequivocal synthetic route to adenine 7-oxide (**7**) has been established. The route started with peroxycarboxylic acid oxidation of 3-benzyladenine (**5**), readily obtainable from adenine (**2**) by benzylation, and proceeded through nonreductive debenzylation of the resulting 3-benzyladenine 7-oxide (**6**).

Adenine (**2**) undergoes *N*-oxidation preferentially at the 1-position, when treated with 30% aqueous H_2O_2 in AcOH at room temperature.[1] This regioselectivity appears to reflect the generalization[2] that on *N*-oxidation pyrimidine compounds form only mono-*N*-oxides, whereas imidazoles are resistant to *N*-oxidation. On the other hand, Rhaese[3] claimed that adenine 7-oxide (**7**) was obtained from **2** in 5% yield by treating it with 0.1 M H_2O_2 in 0.01 M phosphate buffer (pH 7.0) at 37°C for 5 days and that **7** was among the products from X-ray irradiation of **2** in 0.05 M phosphate buffer (pH 7.0). These results were reportedly reproduced by Yamamoto.[4] However, the chemical and spectroscopic evidence adduced by both authors appeared too incomplete to assign the N(7)-oxide structure to their samples which they thought to be **7**, and we completely failed to obtain any *N*-oxides from **2** on repetition of the H_2O_2/buffer oxidation procedure[3] of Rhaese. This led us to devise a three-step route for the synthesis of adenine 7-oxide (**7**) from adenine (**2**) in the present work.

The direct alkylation of **2** at the 3-position in the absence of added base presents the most convenient method of securing 3-alkyladenines (type **5**),[5] and the second stage of alkylation of the 3-substituted adenines (type **5**) provides a ready access to 3,7-disubstituted adenines (type **1**).[5,6] If there would be a parallelism between *N*-alkylation and *N*-oxidation in regioselectivity at the second stage and if a similar two-step reaction sequence involving *N*-oxidation would be coupled with removal of the 3-substituent, it should conclude a synthesis of adenine 7-oxide (**7**). This has now been realized by the use of the benzyl group at the 3-position (Scheme 1).

Treatment of 3-benzyladenine (**5**), obtainable from **2** in 53% yield according to the literature procedure,[5] with magnesium monoperoxyphthalate hexahydrate (MMPP•$6H_2O$)[7] in MeOH at 30°C for 20 h furnished the N(7)-oxide (**6**) in the form of the monohydrate (**6**•H_2O) [mp 262–265°C (decomp.)][8,9] in 40% yield, together with 51% recovery of **5**. Replacement of MMPP•$6H_2O$ by *m*-chloroperoxybenzoic acid (MCPBA) [in MeOH–1 M

acetate buffer (pH 5.0) (1 : 1, v/v), 30°C, 25 h] or by 30% aqueous H_2O_2/$KHCO_3$/MeCN[10] [in MeOH, 25°C, 22 h] in this oxidation also gave **6**•H_2O in 24% (with 29% recovery of **5**) or 12% (with 28% recovery of **5**) yield, respectively. However, the use of 30% aqueous H_2O_2 in AcOH at room temperature or MCPBA in AcOH at 30°C as the oxidizing agent was found to be ineffective. On debenzylation with conc. H_2SO_4 at 35°C for 5 h in the presence of toluene,[6b,11] **6**•H_2O afforded the desired compound (**7**) (mp > 300°C)[12] (**7**•HCl, mp > 300°C) in 55% yield. The correctness of the N(7)-oxide structure of **7** was supported by its uv spectrum[12] that was different from those of the three known isomeric *N*-oxides (adenine 1-oxide,[1] adenine 3-oxide,[13] and 9-hydroxyadenine[14]) and by the following chemical behavior.



Scheme 1

On catalytic reduction (Raney Ni/H_2, H_2O, 1 atm, 50°C, 4 h), **7** produced adenine (**2**) in 92% yield. Treatment of **7** with boiling AcOH for 5 h gave, after recrystallization of the product from 5% aqueous H_2SO_4, 8-oxoadenine sulfate (**3**•1/2H_2SO_4)[15] in 69% yield. The apparent migration of the oxygen function from N(7) to C(8) under acidic conditions is analogous to that observed for guanine 7-oxide[16] and hypoxanthine 7-oxide (**8**).[11d] Deamination of **7** with $NaNO_2$ in aqueous HCl at 90°C provided hypoxanthine 7-oxide (**8**)[11d] and its N(7)→C(8) O-migration product (**4**)[11d] in 4% and 45% yields, respectively.

In addition, methylation of **7** with MeI in $AcNMe_2$ at 25°C for 20 h gave 3-methyladenine 7-oxide dihydrate (**10**•2H_2O) [mp 255–265°C (decomp.)][17] in 25% yield and 7-methoxy-3-methyladenine (**12**), which was isolated in 17% yield in the form of the perchlorate salt (**12**•$HClO_4$) [mp 251–253°C (decomp.)].[18] A similar methylation (25°C, 18 h) converted **10**•2H_2O into **12**•$HClO_4$ in 89% yield. The uv spectrum of **12**•$HClO_4$ was similar to those[6a] of 3,7-dialkyladenine salts. On catalytic reduction (Raney Ni/H_2, H_2O, 1 atm, 40°C, 4 h), **10**•2H_2O and **12**•$HClO_4$ separately produced 3-methyladenine (**11**) in 90% and 73% yields, respectively. On the other hand, treatment of **7** with dimethyl sulfate in 1 N aqueous NaOH at room temperature for 1 h gave **10**•2H_2O and 7-methoxyadenine (**9**) (mp > 300°C)[19] in 23% and 22% yields, respectively. Catalytic hydrogenation (Raney Ni/H_2, H_2O, 1 atm, 40°C, 4 h) of **9** provided adenine (**2**) in 81% yield.

In summary, the above results have established a three-step synthetic route to adenine 7-oxide (**7**) from adenine (**2**) *via* 3-benzyladenine (**5**) and 3-benzyladenine 7-oxide (**6**). The use of the readily removable benzyl group at the 3-position of **2** as a directing group for alteration of regioselectivity in *N*-oxidation has furnished a firm basis for the present successful synthesis of **7**. The location of the oxygen function in **6** and **7** has also been confirmed by preliminary X-ray crystallographic analysis.[20] Since the chemical, chromatographic, and spectroscopic data obtained with our synthetic **7** do not accord with the literature,[3,4] it is hoped that this communication will serve as the first and valid report dealing with the synthesis and characterization of adenine 7-oxide.

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9. Selected spectral data for **6**•H_2O: ms *m/z*: 241 (M^+); uv λ_{max} [95% (v/v) aq. EtOH] 265 nm (ε 12200), 322 (2200); λ_{max} [H_2O (pH 1)] 280 (14700); λ_{max} [H_2O (pH 7)] 262 (12300), 307 (4000); λ_{max} [H_2O (pH 13)] 265 (10700), 296 (sh) (5800); ^1H nmr (Me_2SO-d_6) δ: 5.46 (2H, s, CH_2Ph), 7.27–7.40 and 7.42–7.48 (5H, m, CH_2Ph), 7.97 [1H, s, C(8)-H], 8.09 and 8.91 (1H each, br, NH's), 8.70 [1H, s, C(2)-H]. The assignments of the C(2)-H and C(8)-H signals have been made by comparison with those of the 2-deuterated species.
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12. Selected spectral data for **7**: ms *m/z*: 151 (M^+); uv λ_{max} [95% (v/v) aq. EtOH] 246 nm (sh) (ε 5400), 271 (9100); λ_{max} [H_2O (pH 1)] 274 (11500); λ_{max} [H_2O (pH 7)] 235 (12400), 284 (6100); λ_{max} [H_2O (pH 13)] 235 (13000), 285 (6200); ^1H nmr (Me_2SO-d_6) δ: 7.01 (2H, dull s, NH_2), 8.17 [1H, s, C(2)-H], 8.35 [1H, s, C(8)-H], 12.0–13.0 (1H, br, NH); ^1H nmr (D_2O) δ: 8.26 [1H, s, C(2)-H], 8.29 [1H, s, C(8)-H]. The assignments of the C(2)-H and C(8)-H signals have been made by comparison with those of the 2-deuterated species.
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17. Selected spectral data for **10**•2H_2O: ms *m/z*: 165 (M^+); uv λ_{max} [95% (v/v) aq. EtOH] 263 nm (ε 13100), 316 (3200); λ_{max} [H_2O (pH 1)] 278 (14400); λ_{max} [H_2O (pH 7)] 259 (12100), 303 (4100); λ_{max} [H_2O (pH 13)] 262 (11000), 295 (sh) (5400); ^1H nmr (Me_2SO-d_6) δ: 3.81 [3H, s, N(3)-Me], 7.90 [1H, s, C(8)-H], 8.05 and 8.69 (1H each, br, NH's), 8.38 [1H, s, C(2)-H].
18. Selected spectral data for **12**•$HClO_4$: uv λ_{max} [95% (v/v) aq. EtOH] 281 nm (ε 16200); λ_{max} [H_2O (pH 1)] 278 (15600); λ_{max} [H_2O (pH 7)] 278 (15600); λ_{max} [H_2O (pH 13)] unstable.
19. Selected spectral data for **9**: ms *m/z*: 165 (M^+); uv λ_{max} [95% (v/v) aq. EtOH] 273 nm (ε 9400); λ_{max} [H_2O (pH 1)] 274 (13400); λ_{max} [H_2O (pH 7)] 271 (10200); λ_{max} [H_2O (pH 13)] 273 (10600); ^1H nmr (Me_2SO-d_6) δ: 4.13 (3H, s, OMe), 7.11 (2H, br, NH_2), 8.21 and 8.64 (1H each, s, purine protons).
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