

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

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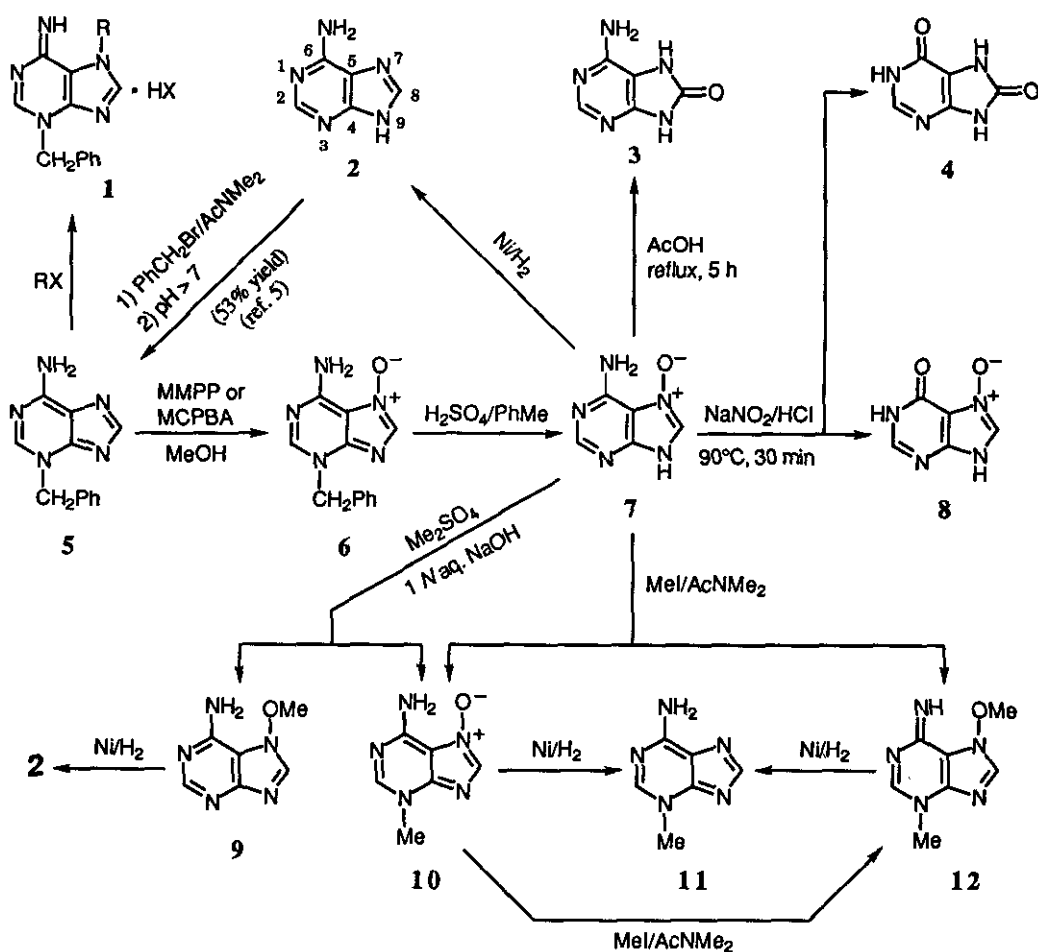
Abstract—The first unequivocal synthetic route to adenine 7-oxide (**7**) has been established. The route started with peroxycarboxylic acid oxidation of 3-benzyladenine (**5**), readily obtainable from adenine (**2**) by benzylation, and proceeded through nonreductive debenylation of the resulting 3-benzyladenine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

Adenine (**2**) undergoes *N*-oxidation preferentially at the 1-position, when treated with 30% aqueous H₂O₂ in AcOH at room temperature.¹ This regioselectivity appears to reflect the generalization² that on *N*-oxidation pyrimidine compounds form only mono-*N*-oxides, whereas imidazoles are resistant to *N*-oxidation. On the other hand, Rhaese³ claimed that adenine 7-oxide (**7**) was obtained from **2** in 5% yield by treating it with 0.1 M H₂O₂ 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 H₂O₂/buffer oxidation procedure³ 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·6H₂O)⁷ in MeOH at 30°C for 20 h furnished the N(7)-oxide (**6**) in the form of the monohydrate (6·H₂O) [mp 262–265°C (decomp.)]^{8,9} in 40% yield, together with 51% recovery of **5**. Replacement of MMPP·6H₂O 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 $\text{H}_2\text{O}_2/\text{KHCO}_3/\text{MeCN}$ ¹⁰ [in MeOH, 25°C, 22 h] in this oxidation also gave $6\cdot\text{H}_2\text{O}$ 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 debenzoylation with conc. H_2SO_4 at 35°C for 5 h in the presence of toluene,^{6b,11} $6\cdot\text{H}_2\text{O}$ afforded the desired compound (7) (mp > 300°C)¹² ($7\cdot\text{HCl}$, mp > 300°C) in 55% yield. The correctness of the *N*(7)-oxide structure of 7 was supported by its uv spectrum¹² that was different from those of the three known isomeric *N*-oxides (adenine 1-oxide,¹ adenine 3-oxide,¹³ and 9-hydroxyadenine¹⁴) and by the following chemical behavior.



Scheme 1

On catalytic reduction (Raney Ni/H₂, H₂O, 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 H₂SO₄, 8-oxoadenine sulfate (**3**·1/2H₂SO₄)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-oxide¹⁶ and hypoxanthine 7-oxide (**8**).^{11d} Deamination of **7** with NaNO₂ 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 AcNMe₂ at 25°C for 20 h gave 3-methyladenine 7-oxide dihydrate (**10**·2H₂O) [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**·HClO₄) [mp 251–253°C (decomp.)].¹⁸ A similar methylation (25°C, 18 h) converted **10**·2H₂O into **12**·HClO₄ in 89% yield. The uv spectrum of **12**·HClO₄ was similar to those^{6a} of 3,7-dialkyladenine salts. On catalytic reduction (Raney Ni/H₂, H₂O, 1 atm, 40°C, 4 h), **10**·2H₂O and **12**·HClO₄ 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**·2H₂O and 7-methoxyadenine (**9**) (mp > 300°C)¹⁹ in 23% and 22% yields, respectively. Catalytic hydrogenation (Raney Ni/H₂, H₂O, 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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REFERENCES AND NOTES

1. (a) M. A. Stevens, D. I. Magrath, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, 1958, **80**, 2755; (b) M. A. Stevens and G. B. Brown, *ibid.*, 1958, **80**, 2759; (c) T. Fujii and T. Itaya, *Tetrahedron*, 1971, **27**, 351; (d) T. Fujii, T. Saito, K. Kizu, H. Hayashibara, Y. Kumazawa, S. Nakajima, and T. Fujisawa, *Chem. Pharm. Bull.*, 1991, **39**, 301.
2. E. Ochiai, 'Aromatic Amine Oxides,' Elsevier, Amsterdam, 1967, pp. 50–51.
3. H.-J. Rhaese, *Biochim. Biophys. Acta*, 1968, **166**, 311.
4. O. Yamamoto, *J. Radiat. Res.*, 1980, **21**, 239.
5. T. Fujii, G. C. Walker, N. J. Leonard, D. C. DeLong, and K. Gerzon, *J. Med. Chem.*, 1979, **22**, 125, and references cited therein.

6. (a) T. Fujii, T. Saito, I. Inoue, Y. Kumazawa, and N. J. Leonard, *Chem. Pharm. Bull.*, 1986, **34**, 1821; (b) N. J. Leonard, T. Fujii, and T. Saito, *ibid.*, 1986, **34**, 2037.
7. P. Brougham, M. S. Cooper, D. A. Cummerston, H. Heaney, and N. Thompson, *Synthesis*, 1987, 1015.
8. Satisfactory analytical and spectroscopic data have been obtained for all of the new compounds reported herein.
9. Selected spectral data for **6**·H₂O: *ms m/z*: 241 (*M*⁺); *uv λ_{max}* [95% (v/v) aq. EtOH] 265 nm (*ε* 12200), 322 (2200); *λ_{max}* [H₂O (pH 1)] 280 (14700); *λ_{max}* [H₂O (pH 7)] 262 (12300), 307 (4000); *λ_{max}* [H₂O (pH 13)] 265 (10700), 296 (sh) (5800); ¹H nmr (Me₂SO-*d*₆) *δ*: 5.46 (2H, s, CH₂Ph), 7.27–7.40 and 7.42–7.48 (5H, m, CH₂Ph), 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.
10. (a) G. B. Payne, P. H. Deming, and P. H. Williams, *J. Org. Chem.*, 1961, **26**, 659; (b) G. B. Payne, *ibid.*, 1961, **26**, 668.
11. (a) L. M. Weinstock, R. J. Tull, A. W. Douglas, and I. Shinkai, *J. Org. Chem.*, 1980, **45**, 5419; (b) K. Ogawa, M. Nishii, J. Inagaki, F. Nohara, T. Saito, T. Itaya, and T. Fujii, *Chem. Pharm. Bull.*, 1992, **40**, 343; (c) *Idem*, *ibid.*, 1992, **40**, 1315; (d) K. Ogawa, M. Nishii, F. Nohara, T. Saito, T. Itaya, and T. Fujii, *ibid.*, 1992, **40**, 612.
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}* [H₂O (pH 1)] 274 (11500); *λ_{max}* [H₂O (pH 7)] 235 (12400), 284 (6100); *λ_{max}* [H₂O (pH 13)] 235 (13000), 285 (6200); ¹H nmr (Me₂SO-*d*₆) *δ*: 7.01 (2H, dull s, NH₂), 8.17 [1H, s, C(2)-H], 8.35 [1H, s, C(8)-H], 12.0–13.0 (1H, br, NH); ¹H nmr (D₂O) *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.
13. I. Scheinfeld, J. C. Parham, S. Murphy, and G. B. Brown, *J. Org. Chem.*, 1969, **34**, 2153.
14. A. A. Watson, *J. Org. Chem.*, 1977, **42**, 1610.
15. T. Fujii and T. Saito, *Chem. Pharm. Bull.*, 1973, **21**, 1954.
16. M. Nishii, J. Inagaki, F. Nohara, K. Isono, H. Kusakabe, K. Kobayashi, T. Sakurai, S. Koshimura, S. K. Sethi, and J. A. McCloskey, *J. Antibiot.*, 1985, **38**, 1440.
17. Selected spectral data for **10**·2H₂O: *ms m/z*: 165 (*M*⁺); *uv λ_{max}* [95% (v/v) aq. EtOH] 263 nm (*ε* 13100), 316 (3200); *λ_{max}* [H₂O (pH 1)] 278 (14400); *λ_{max}* [H₂O (pH 7)] 259 (12100), 303 (4100); *λ_{max}* [H₂O (pH 13)] 262 (11000), 295 (sh) (5400); ¹H nmr (Me₂SO-*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**·HClO₄: *uv λ_{max}* [95% (v/v) aq. EtOH] 281 nm (*ε* 16200); *λ_{max}* [H₂O (pH 1)] 278 (15600); *λ_{max}* [H₂O (pH 7)] 278 (15600); *λ_{max}* [H₂O (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}* [H₂O (pH 1)] 274 (13400); *λ_{max}* [H₂O (pH 7)] 271 (10200); *λ_{max}* [H₂O (pH 13)] 273 (10600); ¹H nmr (Me₂SO-*d*₆) *δ*: 4.13 (3H, s, OMe), 7.11 (2H, br, NH₂), 8.21 and 8.64 (1H each, s, purine protons).
20. T. Date and K. Okamura (Tanabe Seiyaku, Co., Ltd.), personal communication, June 1993.

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