

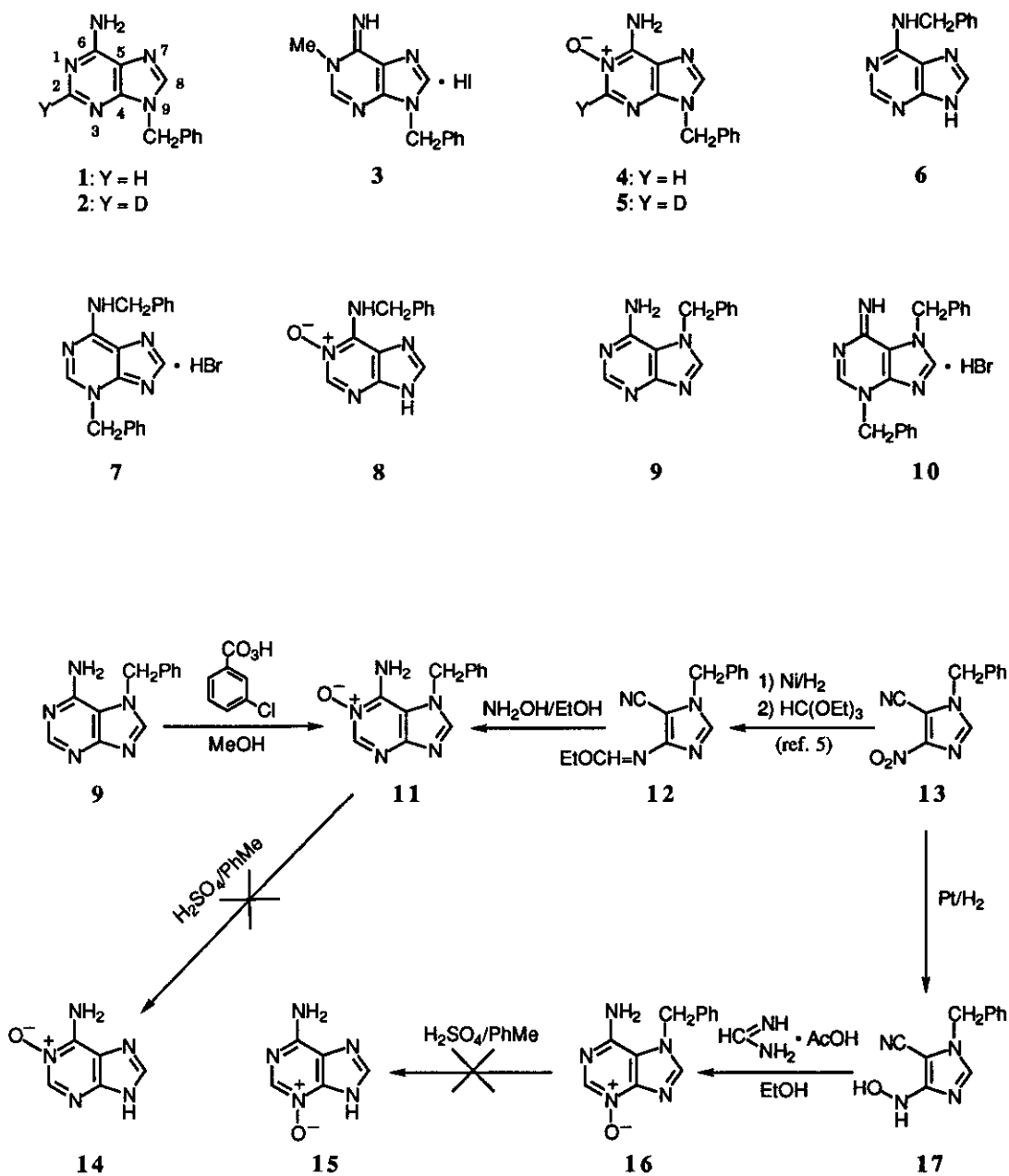
SYNTHESES OF THE N(1)- AND N(3)-OXIDES OF 7-BENZYL-ADENINE

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Abstract—Oxidation of 7-benzyladenine (**9**) with *m*-chloroperoxybenzoic acid in MeOH has been found to yield 7-benzyladenine 1-oxide (**11**) as the main product. Alternatively, the same *N*-oxide (**11**) has been synthesized in 81% yield from 1-benzyl-4-(ethoxymethyleneamino)imidazole-5-carbonitrile (**12**) and hydroxylamine. Treatment of 1-benzyl-4-(hydroxyamino)imidazole-5-carbonitrile (**17**), prepared in 63% yield from the corresponding 4-nitro derivative (**13**) by catalytic reduction (Pt/H₂), with formamidine acetate in boiling EtOH gave 7-benzyladenine 3-oxide (**16**) in 83% yield.

In the *N*^x-monosubstituted adenine series, there is only a partial parallelism in regioselectivity between *N*^y-alkylation and *N*^y-oxidation. 9-Substituted adenines allow both *N*-alkylation¹ and *N*-oxidation² to occur preferentially at the 1-position. For example, methylation of 9-benzyladenine (**1**) with MeI in AcNMe₂ at 50°C for 2 h gives 9-benzyl-1-methyladenine hydriodide (**3**) in 84% yield.^{1d,j} Oxidation of **1** with 30% aqueous H₂O₂ in AcOH at 30°C for 5 days affords 9-benzyladenine 1-oxide (**4**) in 69% yield;^{2d} oxidation of 9-benzyladenine-2-*d* (**2**) with *m*-chloroperoxybenzoic acid (MCPBA) in MeOH at room temperature for 4 h furnishes the corresponding 1-oxide (**5**) in 71% yield.^{2f} In the case of *N*⁶-substituted adenines, alkylation under neutral conditions occurs mainly at the 3-position.³ Whereas benzylation of *N*⁶-benzyladenine (**6**) with PhCH₂Br in AcNMe₂⁴ or HCONMe₂⁵ is no exception



Scheme 1

(i. e., **6** → **7**), oxidation of **6** with MCPBA in MeOH at 30°C for 20 h yields the N(1)-oxide (**8**) as the main product.⁶ Benzylation of 7-benzyladenine (**9**) with PhCH₂Br in AcNMe₂ at 65°C for 16 h to form 3,7-dibenzyladenine hydrobromide (**10**) in 81% yield⁴ is representative of a general 3-alkylation procedure in the 7-substituted adenine series.^{1f,7} Thus, it would be interesting to see whether direct *N*-oxidation of **9** could occur at the 3-position. In the present work, we investigated the MCPBA oxidation of **9** in MeOH.

Oxidation of **9**^{7a,d,8} with MCPBA in MeOH at 23°C for 7 h produced an *N*-oxide [mp 237–242°C (decomp.)]^{9,10} and its *m*-chlorobenzoate salt (mp 193–194°C)¹¹ in 40% and 36% yields, respectively. On neutralization in 50% (v/v) aqueous MeOH with conc. aqueous NH₃, the salt gave the *N*-oxide (in the free base form) in 85% yield. The N(1)-oxide structure (**11**) was assignable to this *N*-oxide on the basis of the following chemical evidence (Scheme 1).

Treatment of 1-benzyl-4-(ethoxymethyleneamino)imidazole-5-carbonitrile (**12**), obtainable from the corresponding 4-nitro derivative (**13**) according to the literature procedure,⁵ with hydroxylamine in EtOH at room temperature for 1 h furnished 7-benzyladenine 1-oxide (**11**) [mp 235–240°C (decomp.)] in 81% yield. This cyclization was analogous to what Yamazaki *et al.*¹² adopted for the synthesis of 2',3'-*O*-isopropylideneadenosine 1-oxide from 5-(ethoxymethyleneamino)-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carbonitrile. On the other hand, catalytic hydrogenation (Pt/H₂, EtOH, 1 atm, room temp., 10 min) of **13** gave the 4-hydroxyamino derivative (**17**) [mp 162–170°C (decomp.)]¹³ in 63% yield. Treatment of **17** with formamidine acetate in boiling EtOH for 3 h provided 7-benzyladenine 3-oxide monohydrate (**16**•H₂O) [mp 225–232°C (decomp.)]¹⁴ in 78% yield. This two-step synthesis of the N(3)-oxide (**16**) from **13** was an application of the method of Taylor and Loeffler,¹⁵ who obtained 7-methyladenine 3-oxide from 1-methyl-4-nitroimidazole-5-carbonitrile through the corresponding 4-hydroxyamino derivative.

Interestingly, the *N*-oxide obtained from **9** by MCPBA oxidation was not identical with the above N(3)-oxide (**16**), but identical with a sample of the N(1)-oxide (**11**) synthesized from **13** through **12**. In an attempt to remove the benzyl group, **11** was treated with conc. H₂SO₄ at 35°C or 50°C for 3 h in the presence of toluene.^{6,8,16} However, no debenylation took place. A similar nonreductive debenylation was also found to be ineffective for **16**.

In summary, the above results reveal that the main product from the MCPBA oxidation of 7-benzyladenine (**9**) is the N(1)-oxide (**11**). This regioselectivity in *N*-oxidation is not in harmony with that^{3,4} in *N*-alkylation. Previously, Stevens and Brown^{2b} reported that the peroxyacetic acid oxidation of 7-methyladenine did not yield an oxide. On the other hand, Scharf and Friedrich¹⁷ reported the monoperoxyphthalic acid oxidations of adenine-cobamide (pseudovitamin B₁₂) and 2-methyladenine-cobamide, 7-substituted adenines linked to cobalt by coordination at the 9-position, in HCONMe₂ to form the corresponding N(1)-oxides in the adenine moiety. However, the chemical and spectral evidence they adduced appears to be somewhat insufficient. Thus, it is hoped that our present work will serve as the first valid example of N(1)-oxidation in the 7-substituted adenine series.

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REFERENCES AND NOTES

1. (a) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 1960, 539; (b) H. G. Windmueller and N. O. Kaplan, *J. Biol. Chem.*, 1961, **236**, 2716; (c) J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, 1963, **85**, 193; (d) N. J. Leonard and T. Fujii, *Proc. Natl. Acad. Sci. U. S. A.*, 1964, **51**, 73; (e) J. A. Montgomery and H. J. Thomas, *J. Org. Chem.*, 1965, **30**, 3235; (f) M. Rasmussen and N. J. Leonard, *J. Am. Chem. Soc.*, 1967, **89**, 5439; (g) E. P. Lira, *J. Heterocycl. Chem.*, 1968, **5**, 863; (h) T. Itaya, F. Tanaka, and T. Fujii, *Tetrahedron*, 1972, **28**, 535; (i) T. Fujii, T. Itaya, and T. Saito, *Chem. Pharm. Bull.*, 1975, **23**, 54; (j) T. Fujii and T. Saito, *ibid.*, 1985, **33**, 3635; (k) T. Fujii, T. Saito, and N. Terahara, *ibid.*, 1986, **34**, 1094.
2. (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) H. Klenow and S. Frederiksen, *Biochim. Biophys. Acta*, 1961, **52**, 384; (d) T. Fujii, C. C. Wu, and T. Itaya, *Chem. Pharm. Bull.*, 1971, **19**, 1368; (e) T. Fujii, T. Saito, and T. Fujisawa,

- Heterocycles*, 1988, **27**, 1163; (f) T. Fujii, T. Saito, K. Kizu, H. Hayashibara, Y. Kumazawa, S. Nakajima, and T. Fujisawa, *Chem. Pharm. Bull.*, 1991, **39**, 301.
3. T. Fujii, T. Saito, and T. Muramoto, *Chem. Pharm. Bull.*, 1983, **31**, 4270, and references cited therein.
 4. J. A. Montgomery and H. J. Thomas, *J. Heterocycl. Chem.*, 1964, **1**, 115.
 5. N. J. Leonard, K. L. Carraway, and J. P. Helgeson, *J. Heterocycl. Chem.*, 1965, **2**, 291.
 6. T. Fujii, K. Ogawa, and T. Itaya, *Heterocycles*, 1994, **37**, 219.
 7. (a) N. J. Leonard and T. Fujii, *J. Am. Chem. Soc.*, 1963, **85**, 3719; (b) A. D. Broom, L. B. Townsend, J. W. Jones, and R. K. Robins, *Biochemistry*, 1964, **3**, 494; (c) N. J. Leonard and M. Rasmussen, *J. Org. Chem.*, 1968, **33**, 2488; (d) T. Fujii, G. C. Walker, N. J. Leonard, D. C. DeLong, and K. Gerzon, *J. Med. Chem.*, 1979, **22**, 125.
 8. N. J. Leonard, T. Fujii, and T. Saito, *Chem. Pharm. Bull.*, 1986, **34**, 2037.
 9. Satisfactory analytical and spectroscopic data have been obtained for all of the new compounds reported herein.
 10. Selected spectral data for this oxide: ms m/z : 241 (M^+); uv $\lambda_{\max}^{95\% \text{ aq. EtOH}}$ 239 nm (ϵ 38300), 285 (7900); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 1) 268 (8500); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 7) 236 (40900), 279 (8200); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 13) 234 (24200), 287 (9700); ^1H nmr ($\text{Me}_2\text{SO}-d_6$) δ : 5.74 (2H, s, CH_2Ph), 7.10–7.16 (2H, m) and 7.25–7.38 (3H, m) (CH_2Ph), 7.89 [2H, br, NH_2], 8.51 and 8.62 (1H each, s, purine protons).
 11. Selected spectral data: ^1H nmr ($\text{Me}_2\text{SO}-d_6$) δ : 5.74 (2H, s, CH_2Ph), 7.1–8.0 (11H, m, aromatic protons and NH_2), 8.51 and 8.61 (1H each, s, purine protons), 13.31 (1H, br, $\text{COO}-\text{H}^+$).
 12. A. Yamazaki, I. Kumashiro, and T. Takenishi, *Chem. Pharm. Bull.*, 1969, **17**, 1128.
 13. Selected spectral data for **17**: ir $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3270, 3140 (NH and OH), 2208 (CN); ^1H nmr ($\text{Me}_2\text{SO}-d_6$) δ : 5.18 [2H, s, $\text{N}(1)-\text{CH}_2\text{Ph}$], 7.2–7.4 [5H, m, $\text{N}(1)-\text{CH}_2\text{Ph}$], 7.84 [1H, s, $\text{C}(2)-\text{H}$], 8.80 (2H, br, NH and OH).
 14. Selected spectral data for **16**• H_2O : ms m/z : 241 (M^+); uv $\lambda_{\max}^{95\% \text{ aq. EtOH}}$ 235 nm (ϵ 18000), 306 (13100); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 1) 226 (12900), 281 (14000); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 7) 233 (18500), 298 (13000); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 13) 232 (17900), 299 (12600); ^1H nmr ($\text{Me}_2\text{SO}-d_6$) δ : 5.75 (2H, s, CH_2Ph), 7.01 (2H, s, NH_2), 7.12–7.21 (2H, m) and 7.25–7.40 (3H, m) (CH_2Ph), 8.34 and 8.53 (1H each, s, purine protons).

15. E. C. Taylor and P. K. Loeffler, *J. Org. Chem.*, 1959, **24**, 2035.
16. (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.
17. H. Scharf and W. Friedrich, *Z. Naturforsch., Teil B*, 1964, **19**, 1043.

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