SYNTHESIS OF HYPOXANTHINE 7-OXIDE, A NEW N-OXIDE AT THE 6-OXO-PURINE LEVEL

Kazuo Ogawa,[†] Tohru Saito,[‡] Fujio Nohara,[†] Masahiro Nishii,[†] Taisuke Itaya,[‡] and Tozo Fujii*,[‡]

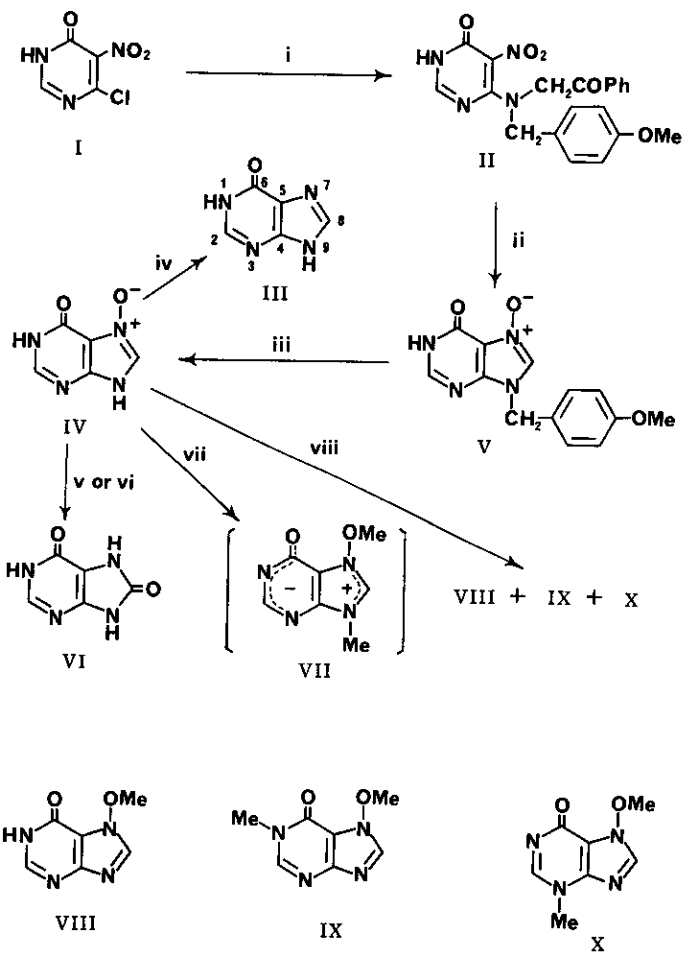
[†]*Research Laboratories, Ikeda Mohando Co., Ltd., Kamiichi-machi, Toyama 930-03, Japan*

[‡]*Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan*

Abstract —— Hypoxanthine 7-oxide (IV) has been synthesized for the first time from 6-chloro-5-nitro-4(3H)-pyrimidinone (I) through the intermediates II and V; catalytic hydrogenolysis, methylation followed by catalytic hydrogenolysis, and isomerization under acidic conditions of IV supported the correctness of the assigned structure.

Among the four possible N-oxides of hypoxanthine (III), the 1-oxide (or the 1-hydroxy tautomer),[1] 3-oxide,[2] and 9-oxide (or the 9-hydroxy tautomer)[3] have been known, but the 7-oxide is hitherto unknown. Our recent success in a stepwise synthesis of guanine 7-oxide,[4] an antitumor antibiotic from Streptomyces sp.,[5] led us to extend such synthetic route to cover the synthesis of this new purine 7-oxide at the hypoxanthine level.

Condensation of 6-chloro-5-nitro-4(3H)-pyrimidinone (I)[6] with ω-(p-methoxybenzylamino)acetophenone gave the 6-(N,N-disubstituted amino)-4-pyrimidone (II), mp 161–163°C (dec.), in 59% yield (Scheme 1).[7] On treatment with aqueous NaOH, II cyclized to afford benzoic acid (59% yield) and 9-(p-methoxybenzyl)hypoxanthine 7-oxide (V) (57%), mp 205–225°C (dec.). Removal of the p-methoxybenzyl group from V furnished the target molecule hypoxanthine 7-oxide (IV) (77%), mp > 300°C; uv λ_{max} [H_2O (pH 1)] 254 nm (ε 9500); λ_{max} [H_2O (pH 7)] 234 (15800), 276 (7100); λ_{max} [H_2O (pH 13)] 230 (13200), 277 (7600); ^1H nmr (1 N D_2SO_4) δ: 8.39 [1H, s, C(2)-H], 9.20 [1H, s, C(8)-H].



SCHEME 1. Reagents and conditions: i, ω-(p-methoxybenzylamino)acetophenone hydrochloride,[4] 1 N aqueous NaOH, EtOH, room temp., 6 h; ii, 2 N aqueous NaOH, room temp., 1 h; iii, 90% aqueous H_2SO_4, toluene, 30°C, 1 h; iv, H_2, Raney Ni, H_2O, 1 atm, 50°C, 4 h; v, AcOH, 95–100°C, 20 h; vi, 2 N aqueous HCl, reflux, 1 h; vii, MeI, $AcNMe_2$, room temp., 12 h; viii, Me_2SO_4, 0.2 N aqueous NaOH, room temp., 2 h.

The correctness of the assigned structure (IV) was supported by the following chemical conversions. On catalytic hydrogenolysis, IV produced hypoxanthine (III) in 82% yield (Scheme 1). Treatment of IV with hot AcOH or boiling aqueous HCl furnished the known isomeric product (VI)[8] in 95% or 50% yield. Methylation of IV with MeI in the absence of alkali gave a complex mixture of products presumed to contain the 7-methoxy-9-methyl derivative VII, and the mixture yielded 9-methylhypoxanthine[9] when subjected to hydrogenolysis (H_2, Raney Ni, 50% aqueous MeOH, 1 atm, 40°C, 3 h). On the other hand, methylation of IV with Me_2SO_4 under alkaline conditions provided 7-methoxyhypoxanthine (VIII), mp 215–218°C (dec.); 7-methoxy-1-methylhypoxanthine (IX), mp 179–180°C; and 7-methoxy-3-methylhypoxanthine (X), mp 175–178°C (dec.), in 28%, 7%, and 3% yields, respectively. Reductive demethoxylations (H_2, Raney Ni, MeOH, 1 atm, 40°C – room temp., 4–8 h) of VIII, IX, and X produced hypoxanthine (III), 1-methylhypoxanthine,[10] and 3-methylhypoxanthine[11] in 81%, 83%, and 66% yields, respectively. The strong uv absorption band at 234 nm described above for IV in H_2O at pH 7 suggests that the neutral species has a considerable population of the N(7)-oxide tautomer in H_2O, as in the case of guanine 7-oxide.[4]

In view of the fact that xanthine 7-oxide is a potent chemical oncogen[12] while guanine 7-oxide is an antitumor agent,[5] evaluation of the N-oxides IV and V for similar biological activities would be of particular interest. Work along this line is in progress in our laboratories.

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REFERENCES

1. (a) E. C. Taylor, C. C. Cheng, and O. Vogl, J. Org. Chem., 1959, 24, 2019; (b) J. C. Parham, J. Fissekis, and G. B. Brown, ibid., 1966, 31, 966; (c) H. Kawashima, T. Meguro, and I. Kumashiro, Bull. Chem. Soc. Jpn., 1966, 39, 633.
2. (a) H. Kawashima and I. Kumashiro, Bull. Chem. Soc. Jpn., 1969, 42, 750; (b) I. Scheinfeld, J. C. Parham, S. Murphy, and G. B. Brown, J. Org. Chem., 1969, 34, 2153.
3. A. A. Watson, J. Org. Chem., 1974, 39, 2911.
4. F. Nohara, M. Nishii, K. Ogawa, K. Isono, M. Ubukata, T. Fujii, T. Itaya, and T. Saito, Tetrahedron Lett., 1987, 28, 1287.

5. (a) D. L. Kern, G. C. Hokanson, J. C. French, and N. K. Dalley, J. Antibiot., 1985, 38, 572; (b) M. Kitahara, K. Ishii, H. Kawaharada, K. Watanabe, T. Suga, T. Hirata, and S. Nakamura, ibid., 1985, 38, 977; (c) M. Nishii, J. Inagaki, F. Nohara, K. Isono, H. Kusakabe, K. Kobayashi, T. Sakurai, S. Koshimura, S. K. Sethi, and J. A. McCloskey, ibid., 1985, 38, 1440.

6. C. Temple, Jr., R. L. McKee, and J. A. Montgomery, J. Org. Chem., 1965, 30, 829.

7. Satisfactory analytical and/or spectroscopic data were obtained for all new compounds described.

8. (a) E. C. Taylor and C. C. Cheng, J. Org. Chem., 1960, 25, 148; (b) F. Bergmann and A. Kalmus, ibid., 1961, 26, 1660.

9. R. K. Robins and H. H. Lin, J. Am. Chem. Soc., 1957, 79, 490.

10. L. B. Townsend and R. K. Robins, J. Org. Chem., 1962, 27, 990.

11. (a) G. B. Elion, J. Org. Chem., 1962, 27, 2478; (b) T. Itaya and H. Matsumoto, Chem. Pharm. Bull., 1985, 33, 2213.

12. K. Sugiura and G. B. Brown, Cancer Res., 1967, 27, 925.

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