

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

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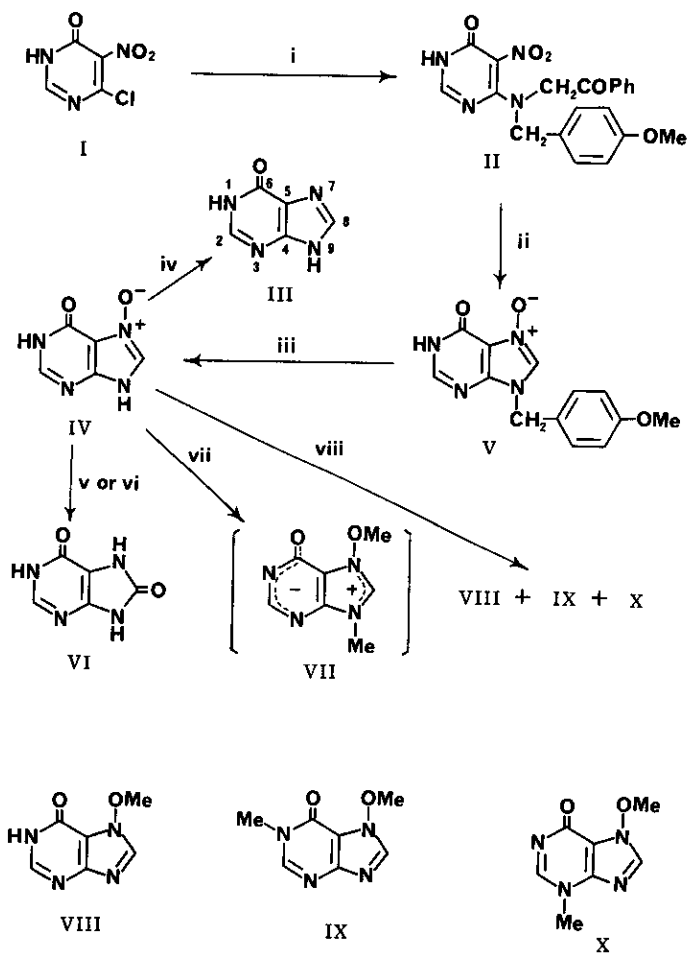
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Abstract — Hypoxanthine 7-oxide (IV) has been synthesized for the first time from 6-chloro-5-nitro-4(3H)-pyrimidinone (I) through the intermediates II and V; catalytic hydrogenolysis, methylation followed by catalytic hydrogenolysis, and isomerization 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-methoxybenzyl-amino)acetophenone gave the 6-(N,N-disubstituted amino)-4-pyrimidinone (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 $\lambda_{\max}$ [H₂O (pH 1)] 254 nm (ϵ 9500); $\lambda_{\max}$ [H₂O (pH 7)] 234 (15800), 276 (7100); $\lambda_{\max}$ [H₂O (pH 13)] 230 (13200), 277 (7600); ¹H nmr (1 N D₂SO₄) δ : 8.39 [1H, s, C(2)-H], 9.20 [1H, s, C(8)-H].



SCHEME 1. Reagents and conditions: i, ω -(p-methoxybenzyl-amino)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-methylhypoxanthine⁹ when subjected to hydrogenolysis (H₂, Raney Ni, 50% aqueous MeOH, 1 atm, 40°C, 3 h). On the other hand, methylation of IV with Me₂SO₄ 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 (H₂, 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-methylhypoxanthine¹¹ in 81%, 83%, and 66% yields, respectively. The strong uv absorption band at 234 nm described above for IV in H₂O at pH 7 suggests that the neutral species has a considerable population of the N(7)-oxide tautomer in H₂O, as in the case of guanine 7-oxide.⁴

In view of the fact that xanthine 7-oxide is a potent chemical oncogen¹² 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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