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

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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 isomeriza-
tion 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-hy-
droxy 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 syn-
thesis 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-pyrimidone (II), mp 161-
163°C (dec.), in 59% yield (Scheme 1). 7 On treatment with aqueous NaOH, II cy-
clized 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 λmax
[H2O (pH 1)] 254 nm (ε 9500); λmax [H2O (pH 7)] 234 (15800), 276 (7100); λmax [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, \( \omega-\text{(p-methoxybenzyl-}
\text{amino) acetophenone hydrochloride,} \) \( ^4 \) \( 1 \text{ N aqueous NaOH, EtOH,}
\text{room temp., 6 h; ii, 2 N aqueous NaOH, room temp., 1 h;}
\text{iii, 90\% aqueous H}_2\text{SO}_4, \text{toluene, 30°C, 1 h; iv, H}_2, \text{ Raney}
\text{Ni, H}_2\text{O, 1 atm, 50°C, 4 h; v, AcOH, 95–100°C, 20 h; vi, 2}
\text{N aqueous HCl, reflux, 1 h; vii, MeI, AcNMe_2, room temp.,}
\text{12 h; viii, Me}_2\text{SO}_4, \text{0.2 N aqueous NaOH, room temp., 2 h.} \)
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) 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 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 demethoxylation (H₂, Raney Ni, MeOH, 1 atm, 40°C–room temp., 4–8 h) of VIII, IX, and X produced hypoxanthine (III), 1-methylhypoxanthine, and 3-methylhypoxanthine 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.

In view of the fact that xanthine 7-oxide is a potent chemical oncogen while guanine 7-oxide is an antitumor agent, 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.

ACKNOWLEDGMENT We thank Messrs. Kado Ikeda, Kaju Ikeda, and Koji Kika (Ikeda Mohando Co., Ltd.) for support.

REFERENCES


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


Received, 17th December, 1987