SYNTHESIS OF 6-IMINO-1,9-DIMETHYL-8-OXOPURINE, A CONSTITUENT OF THE MARINE SPONGE HYMENIACIDON SANGUINEA GRANT

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Abstract — The marine 8-oxopurine I was synthesized from 8-bromo-9-methyl adenine (VI) through the intermediates VII·HI and VII or, more effectively, through 6-amino-9-methyl-8-oxopurine (VIII). The N⁴-acetyl derivative II and the rearranged isomer X were also prepared.

The title compound 6-imino-1,9-dimethyl-8-oxopurine (I) and 1-methyladenine (spongopurine¹) (III), new and known adenine derivatives, were recently isolated, but only in the form of the acetyl derivatives (II and acetylspongopurine), by Cimino et al.² from the English Channel sponge Hymeniacidon sanguinea Grant. Although the new acetyl derivative II was fully characterized by means of spectroscopic and X-ray crystallographic analyses, the parent base I remained unknown because of the difficulty in separating I and III from each other at the free base level.² This led us to secure the base I itself by synthesis.³

\[ \text{I: } R = H \]
\[ \text{II: } R = \text{COMe} \]

Bromination of 9-methyladenine (V)⁴ with Br₂ in 0.5 M acetate buffer (pH 4) was carried out in a manner similar to that reported by Ikehara et al.,⁵ giving the 8-bromo derivative VI, mp 274–275°C (dec.) [lit.⁵b mp 229°C (dec.)], in 87% yield. On methylation with MeI in AcNMMe₂ at 50°C for 3.5 h, VI afforded the 1-methylated product VII·HI, mp 244–246°C (dec.),⁶ in 99% yield. The salt VII·HI was converted into the free base VII [80% yield; mp 216.5–218°C; nmr (Me₂SO-d₆) δ: 3.44 and 3.59 (3H each, s, NMe's), 7.23 (1H, br, NH), 8.09 (1H, s, C(2)-H)] by treatment with 10% aqueous Na₂CO₃. On the other hand, VII·HI underwent Dimroth rearrangement⁷ in warm 1 N aqueous NaOH (55°C, 35 min) to furnish the N⁴,9-dimethyl isomer IX [88%; mp 186.5–188°C; nmr (Me₂SO-d₆) δ: 2.96 (3H, d,
\[ J = 4 \text{ Hz, } \text{NMe} \], 3.66 (3H, s, N(9)-Me), 7.83 (1H, br, NHMe), 8.21 (1H, s, C(2)-H). The formation of the above two isomeric products (VII and IX) from VII·HI under different alkaline conditions supported the correctness of the 1,9-dimethyl structure of VII and hence that of VII·HI.

Treatment of VII with NaOAc in boiling AcOH for 5 h gave the target compound I [36%; mp >300°C; ir \( \nu_{\text{Nujol}} \) 1694 cm\(^{-1}\) (8-oxo); nmr (\( CD_3 CO_2 D \)) \( \delta : 3.66 \) and 4.10 (3H each, s, NHMe's), 8.58 (1H, s, C(2)-H)] together with the N'-acetyl derivative I\( I' \) [34%; mp 248-249.5°C (dec.) (lit. \(^2\) mp 245-246°C)].

The uv, ir, and nmr spectral data obtained for the synthetic I were in agreement with those reported \(^2\) for the "natural" sample. The above transformation of the 8-bromo function into the 8-oxo function has a precedent in which Ikehara and Kaneko \(^9\) prepared 8-oxoadenosine derivatives from 8-bromoadenosine derivatives. Attempts to obtain I from II by hydrolysis were unsuccessful. The 1,9-dimethyl structure of I was confirmed by acetylation (Ac\(_2\)O/pyridine, reflux, 10 min) to give II (81% yield) and by the Dimroth rearrangement (1 N aq. NaOH, reflux, 1 h) to yield 9-methyl-6-methylamino-8-oxopurine (X) [91%; mp >300°C; ir \( \nu_{\text{Nujol}} \) max 1695 cm\(^{-1}\) (8-oxo); nmr (Me\(_2\)SO-d\(_6\)) \( \delta : 2.94 \) (3H, d, \( J = 5 \text{ Hz, NMe} \), 3.22 (3H, s, N(9)-Me), 6.39 (1H, q, \( J = 5 \text{ Hz, NHMe} \), 8.10 (1H, s, C(2)-H), 10.07 (1H, dull, 10.07 (1H, dull, ...
N(7)-H), which was identical with a sample obtained from IX in 72% yield by treatment with boiling 1 N aqueous NaOH for 1.5 h.

Finally, the following alternative synthesis of I was found to be more straightforward and simple to operate and gave a better result. Treatment of VI with 1 N aqueous NaOH (reflux, 1.5 h) afforded 6-amino-9-methyl-8-oxopurine (VIII) [97%; mp >300°C; ir: $\nu_{\text{max}}^{\text{Nujol}}$ 1712 cm$^{-1}$ (8-oxo); nmr (Me$_2$SO-d$_6$) $\delta$: 3.22 (3H, s, N(9)-Me), 6.35 (2H, dull, NH$_2$), 8.01 (1H, s, C(2)-H), 10.09 (1H, dull, NH)].

Methylation of VIII with MeI in AcMe$_2$N (50°C, 7 h) gave, after basification, the desired compound I in 75% yield.

In summary, the results of the above synthesis have allowed us to fully characterize compound I itself, forestalling the unrealized isolation of this substance from the natural source. It is well known that an alkyl group at the 9-position of adenine orients further alkylation to the 1-position to form 1,9-di-alkyladenine (type IV).$^{10}$ Interestingly, such directivity in alkylation also holds in the cases of the 8-bromo and 8-oxo derivatives (VI and VIII).

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REFERENCES

6. Satisfactory analytical and/or spectroscopic data were obtained for all new compounds described.
8. Uv spectral data for I: $\lambda_{\text{max}}$ 95% aq. EtOH 221.5 nm (ε 22000), 291.5 (12300); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 1) 221 (28000), 278 (10400); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 7) 220 (24500), 285 (12000); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (pH 13) 280 (14600), 310 (ah) (4800).


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