

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

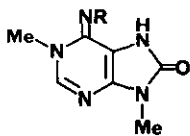
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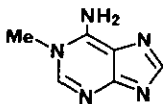
Abstract — The marine 8-oxopurine I was synthesized from 8-bromo-9-methyladenine (VI) through the intermediates VII·HI and VII or, more effectively, through 6-amino-9-methyl-8-oxopurine (VIII). The N^6 -acetyl derivative II and the rearranged isomer X were also prepared.

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 Hymeniacion 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

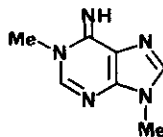


I: R = H

II: R = COMe



III



IV

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 AcNMe₂ 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 N^6 ,9-dimethyl isomer IX [88%; mp 186.5–188°C; nmr (Me₂SO-d₆) δ: 2.96 (3H, d,

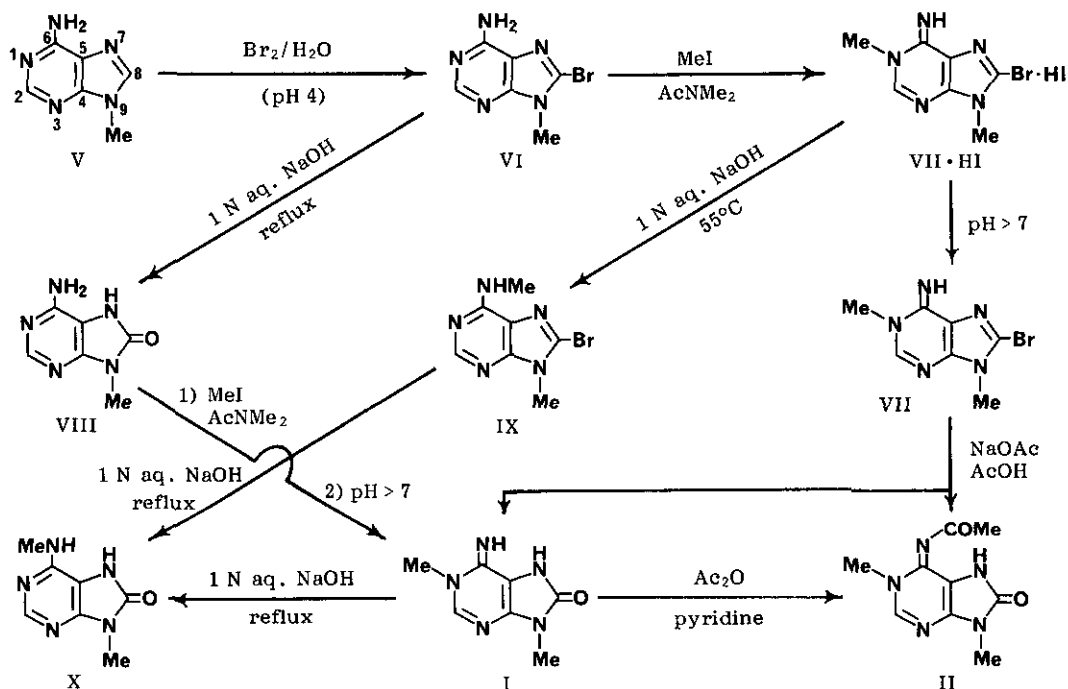


Chart 1

\underline{J} = 4 Hz, NHMe), 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; $\nu_{\text{max}}^{\text{Nujol}}$ 1694 cm^{-1} (8-oxo); nmr ($\text{CF}_3\text{CO}_2\text{D}$) δ : 3.66 and 4.10 (3H each, s, NMe's), 8.58 (1H, s, C(2)-H)]⁸ together with the N⁶-acetyl derivative II [34%; mp 248–249.5°C (dec.) (lit.² mp 245–246°C)].

The uv, ir, and nmr spectral data obtained for the synthetic II were in agreement with those reported² for the "natural" sample. The above transformation of the 8-bromo function into the 8-oxo function has a precedent in which Ikehara and Kaneko⁹ prepared 8-oxyadenosine 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_2O /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; $\nu_{\text{max}}^{\text{Nujol}}$ 1695 cm^{-1} (8-oxo); nmr ($\text{Me}_2\text{SO}-d_6$) δ : 2.94 (3H, d, \underline{J} = 5 Hz, NHMe), 3.22 (3H, s, N(9)-Me), 6.39 (1H, q, \underline{J} = 5 Hz, NHMe), 8.10 (1H, s, C(2)-H), 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 $\nu_{\max}^{\text{Nujol}}$ 1712 cm^{-1} (8-oxo); nmr ($\text{Me}_2\text{SO}-d_6$) δ : 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 AcNMe_2 (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-dialkyladenine (type IV).¹⁰ Interestingly, such directivity in alkylation also holds in the cases of the 8-bromo and 8-oxo derivatives (VI and VIII).

ACKNOWLEDGMENT

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3. Presented in part at the 73rd Meeting of the Hokuriku Branch, Pharmaceutical Society of Japan, Toyama, November 14, 1987.
4. (a) T. Fujii, S. Sakurai, and T. Uematsu, Chem. Pharm. Bull., 1972, 20, 1334; (b) M. Hedayatullah, J. Heterocycl. Chem., 1982, 19, 249.
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7. For the Dimroth rearrangement of 1,9-disubstituted adenines, see T. Fujii and T. Saito, Chem. Pharm. Bull., 1985, 33, 3635, and earlier references cited therein.
8. Uv spectral data for I: $\lambda_{\max}^{95\% \text{ aq. EtOH}}$ 221.5 nm (ϵ 22000), 291.5 (12300); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 1) 221 (28000), 278 (10400); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 7) 220 (24500), 285 (12000); $\lambda_{\max}^{\text{H}_2\text{O}}$ (pH 13) 280 (14600), 310 (sh) (4800).

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