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

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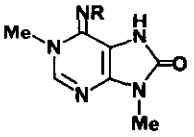
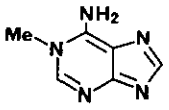
Abstract —— The marine 8-oxopurine I was synthesized from 8-bromo-9-methyladenine (VI) through the intermediates VII·HI and VII or, more effectively, through 6-amino-9-methyl-8-oxopurine (VIII). The N^6-acetyl derivative II and the rearranged isomer X were also prepared.

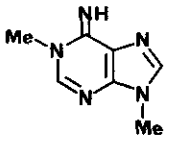
The title compound 6-imino-1,9-dimethyl-8-oxopurine (I) and 1-methyladenine (spongopurine[1]) (III), new and known adenine derivatives, were recently isolated, but only in the form of the acetyl derivatives (II and acetylspongopurine), by Cimino et al.[2] from the English Channel sponge Hymeniacidon 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]



I: R = H
II: R = COMe



III



IV

Bromination of 9-methyladenine (V)[4] with Br_2 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 $AcNMe_2$ 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 (Me_2SO-d_6) 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 Na_2CO_3. On the other hand, VII·HI underwent Dimroth rearrangement[7] 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 (Me_2SO-d_6) δ: 2.96 (3H, d,

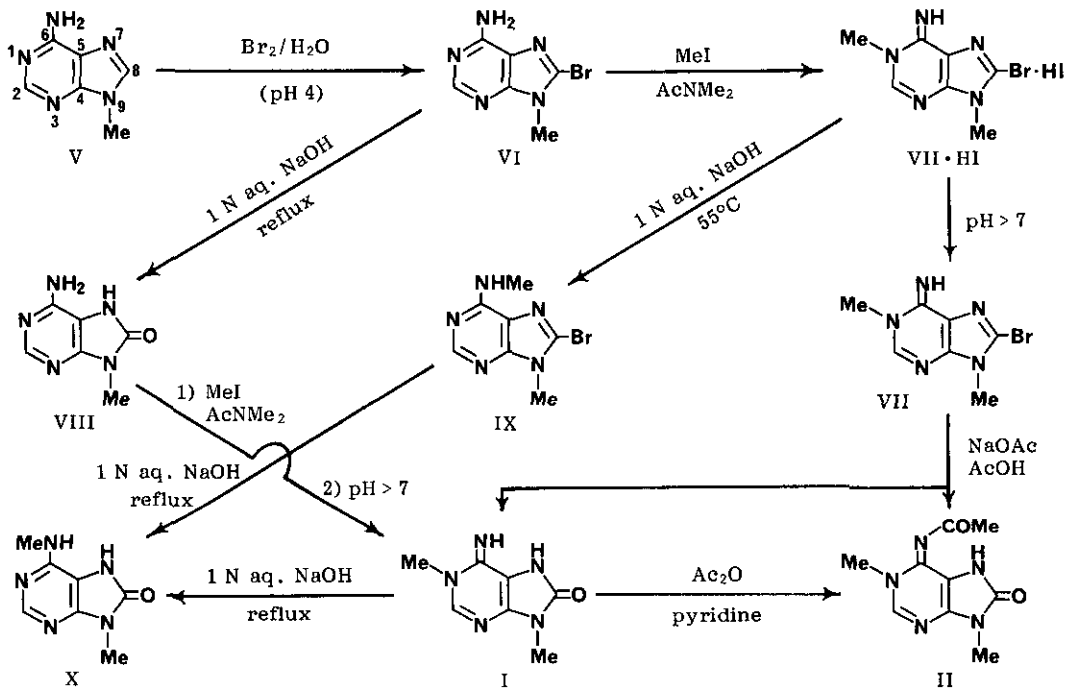


Chart 1

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; ir ν_{max}^{Nujol} *1694 cm^{-1} (8-oxo); nmr (CF_3CO_2D) δ: 3.66 and 4.10 (3H each, s, NMe's), 8.58 (1H, s, C(2)-H)*][8] together with the N^6-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 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-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; ir ν_{max}^{Nujol} 1695 cm^{-1} (8-oxo); nmr (Me_2SO-d_6) δ: 2.94 (3H, d, J = 5 Hz, NHMe), 3.22 (3H, s, N(9)-Me), 6.39 (1H, q, 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 ν_{max}^{Nujol} 1712 cm^{-1} (8-oxo); nmr (Me_2SO-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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8. Uv spectral data for I: $\lambda_{max}^{95\%\ aq.\ EtOH}$ 221.5 nm (ε 22000), 291.5 (12300); $\lambda_{max}^{H_2O}$ (pH 1) 221 (28000), 278 (10400); $\lambda_{max}^{H_2O}$ (pH 7) 220 (24500), 285 (12000); $\lambda_{max}^{H_2O}$ (pH 13) 280 (14600), 310 (sh) (4800).

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