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SYNTHESIS OF 3-METHYLISOGUANOSINE, A POSITIONAL ISOMER OF PHARMACOLOGICALLY ACTIVE NUCLEOSIDES FROM MARINE ANIMALS

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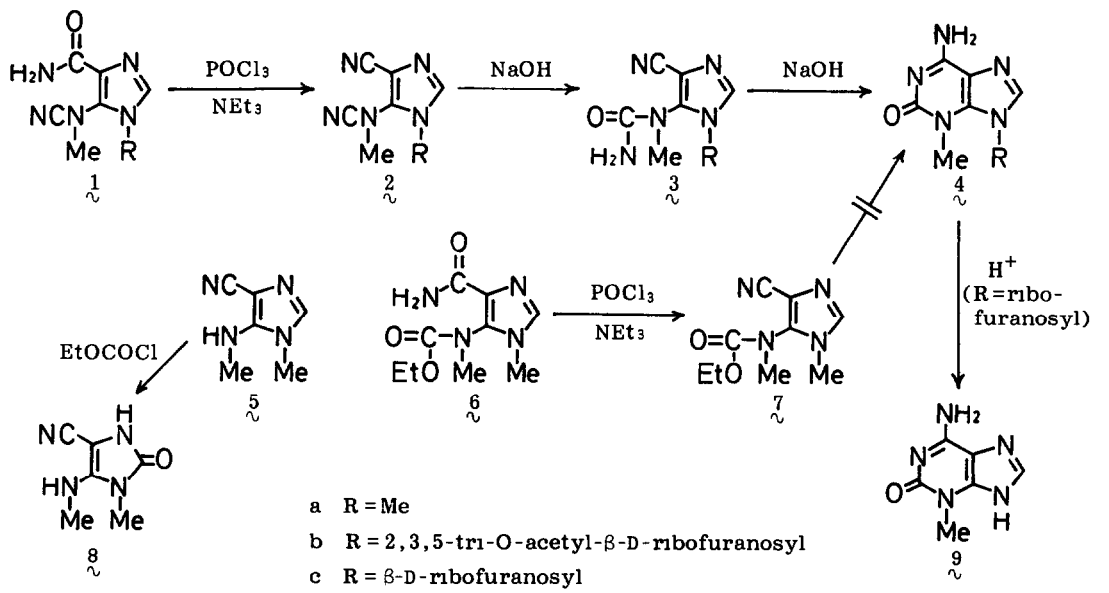
Abstract——3-Methylisoguanosine (4c) has been synthesized from 5-(cyanomethylamino)-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide (1b) through the carbonitrile (2b)

The biologically active substance from the marine sponge Tedania digitata[1] and from the marine nudibranch Anisodoris nobilis[2] has recently been identified as 1-methylisoguanosine Spongosine (O^2-methylisoguanosine) from the marine sponge Cryptotethia crypta[3] also has been shown to have muscle relaxant, anti-inflammatory, and other pharmacological activities [4] These findings suggest the occurrence of other N-methyl isomers of isoguanosine in marine organisms and their biological activities Of so far unknown 7- and 3-methylisoguanosine (4c),[5] we have been more interested in 4c in connection with our current studies on the hydrolysis of the glycosidic bonds of 3-methyl-9-β-D-ribofuranosylpurines [6] This paper describes the first synthesis of 4c

Methylation of isoguanosine was reported not to give 4c [2b,3b] The glycosidic bond of 4c was expected to be so labile in analogy with those of known 3-methyl-9-β-D-ribofuranosylpurines[6,8] that the reported methods of preparing 3,9-dimethylisoguanine (4a)[7] seemed inapplicable to the synthesis of 4c We, therefore, desired to develop a new synthetic route to 4a adaptable to the nucleoside level. When the imidazolecarbonitrile (5)[1b,9] was treated with EtOCOCl in acetate buffer



a R = Me
b R = 2,3,5-tri-O-acetyl-β-D-ribofuranosyl
c R = β-D-ribofuranosyl

(pH 5),[6d] the product obtained was not the desired 7 but 8, mp 240–241° (dec.) [10] Compound 7 was produced as an oil by dehydration of 6[6d, 11] with $POCl_3$ However, several attempts to convert 7 into 4a failed. Treatment of 1a[6a, 11] with $POCl_3$ in $CHCl_3$ in the presence of NEt_3 at room temperature gave 2a, mp 55–57°, in 72% yield On treatment with 0 1 N aq. NaOH at room temperature, 2a was transformed into 3a, mp 187–188°, which then cyclized under the reaction conditions to 4a, mp >300°, in 94% overall yield, δ (DMSO-d_6) 3 64 (3H, s, N(3)-Me), 3 94 (3H, s, N(9)-Me), 7 64 (1H, s, C(8)-H) The UV spectra of 4a matched with the reported data [7a]

According to this model experiment, 1b[6a] was converted into 2b (an oil) and treatment of 2b with 0 1 N aq NaOH gave 4c as monohydrate, mp 175–178° (dec.), in 37% overall yield, $\lambda_{max}^{H_2O}$ (pH 2) 238 nm (ε 7000), 285 (13400), $\lambda_{max}^{H_2O}$ (pH 7) 280 (11500), $\lambda_{max}^{H_2O}$ (pH 13) 280 (11800), δ (DMSO-d_6) 3 62 (3H, s, N(3)-Me), 6 01 (1H, d, J = 5 Hz, C(1')-H), 7 37 (2H, b, NH_2), 8 08 (1H, s, C(8)-H) The structure of 4c was assigned on the basis of UV and NMR spectral similarity to 4a and by its hydrolysis (with 0 1 N aq HCl at room temperature for 15 h) that gave 3-methylisoguanine (9)[7a] in 60% yield The glycosidic bond of 4c proved to be susceptible to acidic hydrolysis as expected, but was found to be stabler than any of other 3-methyl-9-β-D-ribofuranosylpurines [6,8] 4c underwent hydrolysis in 0 1 N aq HCl at 25° at a rate (pseudo-first-order rate constant, 1 7 x 10^{-2} min^{-1}) about 60 times smaller than that of its isomer, 3-methylguanosine [6c]

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