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3-Methylpurine (I)

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Sir:

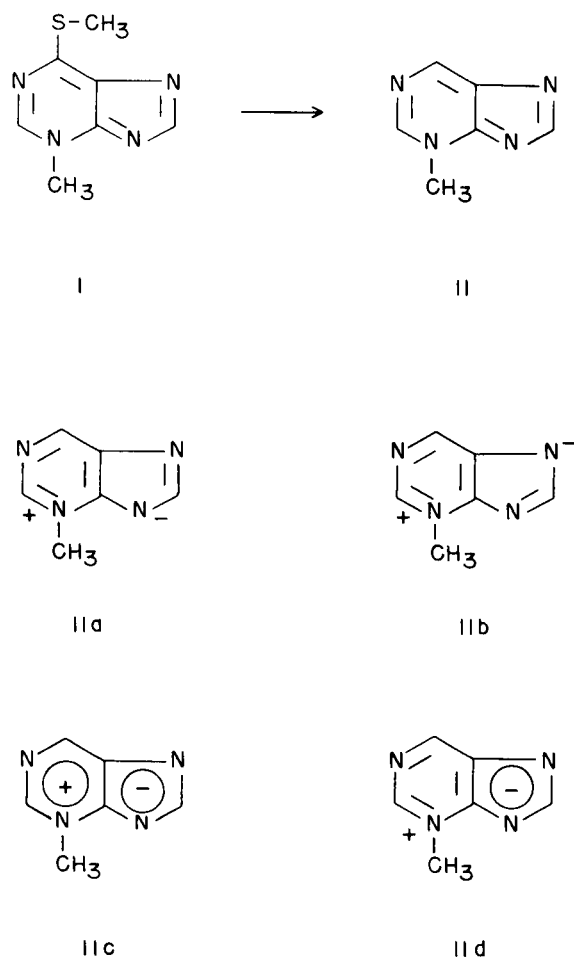
We wish to report the successful preparation and isolation of the only remaining undescribed *N*-methyl isomer of purine, 3-methylpurine. It has been suggested that 7- and 9-methylpurine (2-4) should be more stable than 1- or 3-methylpurine since the methyl group in 7- and 9-methylpurine simply replaces the proton on an imidazole nitrogen whereas a methyl group on a nitrogen in the pyrimidine moiety produces a new unusual quinoid type structure. This increased reactivity has been demonstrated (5) by the increase in ease of nucleophilic displacement of an alkylthio group in 1-methylpurine derivatives as compared with the corresponding 7- and 9-methylpurine derivatives. The ease of nucleophilic displacement which occurs in 3-methylpurine derivatives has also been well documented (6, 7, 9) and is equal to or greater than that which occurs in the 1-methylpurine series. Although Raney Nickel dethiation of 1-methyl-6-purinethione produced 1-methylpurine (5) in crystalline form, several unsuccessful attempts at the preparation of 3-methylpurine by dethiation of 3-methyl-6-purinethiol, 3-methyl-6-methylthiopurine, 3-methyl-2,6-purinedithiol and dehalogenation of 6-chloro-3-methylpurine have been reported (7-9). The preparation of 3-ethylpurine has also been unsuccessful (10).

It is of interest that a compound isolated (11) from *Agaricus Nebularis Batsch* was subsequently characterized (12) as 9-(β -D-ribofuranosyl)purine (Nebularine), an *N*-substituted purine.

The isolation (13-14) and characterization of other naturally occurring compounds as 3-substituted purine derivatives has focused attention on 3-methylpurines as model compounds. Indeed glycosidation previously assigned to position 7 has recently been shown (15) to be at position 3 in synthetic 6-dimethylaminopurine nucleosides related to puromycin. Recent glycosylation studies of purine itself (16, 17) could not unequivocally exclude position 3 as a possible site of glycosidation due to the fact that no model 3-alkylpurine is known. Thus the preparation of 3-methylpurine (II) was investigated in our Laboratory.

3-Methyl-6-methylthiopurine (7, 18) (I, 0.5 g.) was dissolved in hot methanol and methanol washed Raney Nickel (19) was added to the clear solution. The rate of dethiation was followed by a frequent ultraviolet absorption spectrum survey on the reaction mixture. When the absorption band assigned to the methylthio group (312 m μ) had completely disappeared, with the concomitant appearance of a new

absorption band at a shorter wave length (277 m μ), the catalyst was removed and the filtrate evaporated to dryness *in vacuo* as quickly as possible. The residue was recrystallized from a *n*-heptane-benzene mixture to afford 0.2 g. of 3-methylpurine (II), m.p. 184-185° dec. *Anal.* Calcd. for C₆H₆N₄: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.77; H, 4.55; N, 41.75. The ultraviolet absorption spectra exhibited λ max (pH 1), 275 (ϵ , 9,780); λ max (MeOH), 277 (ϵ , 6,950); λ max (pH 11), 276 (ϵ , 6,980) and λ min (pH 1), 231 (ϵ , 1,200); λ min (MeOH), 238 (ϵ , 670); λ min (pH 11), 237 (ϵ , 1,070). The p.m.r. spectrum in DMSO-d₆ with tetramethylsilane as an internal standard exhibited absorption peaks at 4.3 δ (3-protons, singlet), 8.45 δ (1-proton, singlet), 9.025 δ (1-proton, singlet) and 9.1 δ (1-proton, singlet). The instability of II toward alkali



was confirmed since a rapid (less than 2 minutes) disappearance of the ultraviolet absorption band at $277\text{ m}\mu$ was observed in 1 *N* sodium hydroxide solution. However, II was found to be stable, as judged by ultraviolet absorption, in a pH 11 buffer for a period of at least 24 hours. The contributions made by structures IIa, IIb, IIc and IId could explain the increased reactivity which has been observed for 3-methylpurine derivatives (6, 8). The contribution of such charged species to the over-all structure is strongly supported by p.m.r. spectral data. One aromatic proton (probably the C₈ proton) is found upfield (8.45 δ) from the other two essentially equivalent aromatic protons (9.02 δ and 9.1 δ). This would suggest delocalization of the positive charge in the pyrimidine ring as in IIc and would suggest increased electron density at C₈. The deshielding of the methyl group (4.3 δ) as compared with the *N*-methyl absorption peak for 7-methylpurine (4.05 δ) and 9-methylpurine (3.9 δ) is support for the lack of electrons in the pyrimidine ring.

It is of interest that 3-methylpurine is stable at ordinary temperature for a period of at least 8 months. 3-Methylpurine does darken slightly with time but was still essentially analytically pure as judged by ultraviolet absorption spectra and TLC chromatography. This same observation of darkening on storage has been previously reported (2) for 9-methylpurine. 1-Methylpurine (5) has also been found to decompose slowly over a prolonged period of time when stored in our Laboratory.

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