# Synthesis of 3,9-Dimethyl- and 3-Methyl-9-ethyl-adenine *via* *N'*-Alkoxy-1-alkyl-5-formamidoimidazole-4-carboxamidine

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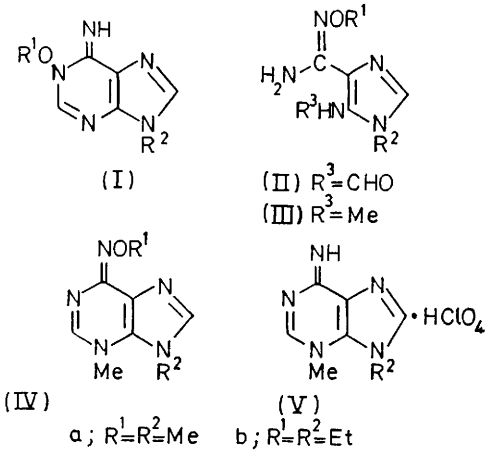
*Summary* 3,9-Dimethyl- and 3-methyl-9-ethyl-adenine have been synthesized from *N'*-alkoxy-1-alkyl-5-formamidoimidazole-4-carboxamidine (II) by reduction with $LiAlH_4$ followed by cyclisation with ethyl orthoformate and removal of the alkoxy-group by catalytic hydrogenolysis.

3,9-DISUBSTITUTED adenines have previously been prepared as cyclic derivatives[1] or $N^6N^6$-dialkyl derivatives.[1b,2] We now describe a general method for the synthesis of substituted adenines of type (V) which utilizes the imidazole (II),[3] the readily isolable intermediate in the Dimroth rearrangement of 1-alkoxy-9-alkyladenine (I),[4] as a starting material.

On treatment with $LiAlH_4$ in tetrahydrofuran at room temperature, the methyl analogue (IIa)[3] produced the methylamino-derivative (IIIa)† (74%)‡ m.p. 135—136°. The hydrochloride, m.p. 180—182° (decomp.), of (IIIa) was then heated in ethyl orthoformate to give the cyclised product (IVa) (73%), m.p. 266·5—267° (decomp.). Hydrogenolysis of the perchlorate, m.p. 244—245° (decomp.), of (IVa) using 10% Pd–C and $H_2$ furnished 3,9-dimethyladenine perchlorate (Va) (26%), m.p. 333—334° (decomp.); $\lambda_{max}$ (95% EtOH) 272 nm ($\epsilon$ 12,900); $\lambda_{max}$ ($H_2O$) (pH 1) 270 (15,600); $\lambda_{max}$ ($H_2O$) (pH 7) 270 (15,400); $\lambda_{max}$ ($H_2O$) (pH 13) unstable; $\tau$ [$(CD_3)_2SO$] 5·91 (3H, s, $N^{(9)}$-Me), 5·82 (3H, s, $N^{(3)}$-Me), 1·71 and 1·44 (1H each, s, purine protons), 0·94 and 0·88 (2H, $=N^+H_2$ or two NH's). The u.v. spectra of 2',3'-*O*-isopropylidene-3,5'-cycloadenosine perchlorate [m.p. 277—278° (decomp.)], prepared from the corresponding *p*-toluenesulphonate,[1a] compare favourably with those of (Va).

Replacement of (IIa) by the ethyl analogue (IIb)[3] in the reaction sequence described above provided (IIIb) (78%), m.p. 89—91°, (IVb)·$H_2O$ (58%), m.p. 245—248° (decomp.), (IVb)·$HClO_4$ (93%), m.p. 180—181° (decomp.), and 9-ethyl-3-methyladenine perchlorate (Vb) (14%), m.p. 294·5—295° (decomp.).




The present synthesis affords another example of the usefulness of the 1-alkoxy-group as in (I) for chemical modification of the adenine ring.[3,5]

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† All new compounds gave satisfactory analyses.

‡ Yields are based on product samples shown to be homogeneous by paper or thin-layer chromatography.

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