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A GENERAL SYNTHETIC ROUTE TO 3,9-DIALKYLADENINES AND THEIR RING OPENING

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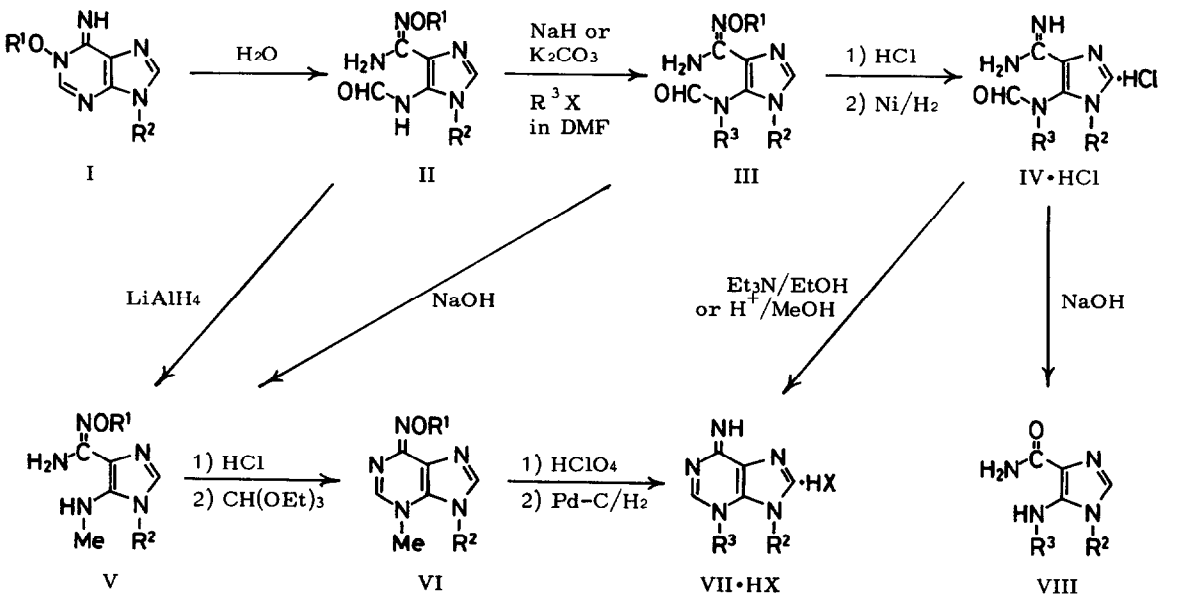
3,9-Disubstituted adenines (type VII) are among the eleven possible N^x,N^y-disubstituted adenine isomers, and they have been prepared as cyclic derivatives,[1-4] N^6,N^6-dialkyl derivatives,[2,5-8] or an N^6-monomethylated derivative.[9] It was not until in relatively recent years, however, that their prototype, 3,9-dimethyladenine (VII, $R^2 = R^3 = Me$), could be synthesized.[10] The synthesis consisted of the $LiAlH_4$ reduction of the formamidoimidazole (II, $R^1 = R^2 = Me$), the readily isolable intermediate[11] in the Dimroth rearrangement of 1-methoxy-9-methyladenine (I, $R^1 = R^2 = Me$),[12] followed by cyclization with ethyl orthoformate and removal of the methoxyl group by catalytic hydrogenolysis (II → V → VI → VII·$HClO_4$ in Scheme 1). Although this method has been shown to be applicable to synthesis of 3-methyl-9-alkyladenines (VII, R^2 = alkyl; $R^3 = Me$) by the parallel synthesis of 3-methyl-9-ethyladenine (VII, $R^2 = Et$; $R^3 = Me$)[10] starting with II ($R^1 = R^2 = Et$), it suffers from the intrinsic defect that the 3-substituent (R^3) of the resulting 3,9-disubstituted adenines (type VII) is confined to only the methyl group. We have now removed such a drawback with a general synthetic route established newly.



Scheme 1

Methylation of the Na salt of II ($R^1 = R^2 = Me$), generated in situ from the corresponding formamido derivative (II, $R^1 = R^2 = Me$)[11a] and NaH in N,N-dimethylformamide (DMF), with MeI (DMF, room temp., 2 hr) afforded the N-methylformamido derivative (III, $R^1 = R^2 = R^3 = Me$) [mp 162–163°; UV $\lambda^{95\%\ EtOH}_{shoulder}$ 250 nm (ε 5510); $\lambda^{H_2O}_{max}$ (pH 1) 253 (7630); $\lambda^{H_2O}_{shoulder}$ (pH 7) 250 (5680); $\lambda^{H_2O}_{shoulder}$ (pH 13) 250 (5680)][13] in 87% yield. Apart from this favorable result, the unusually strong acidity (pK_a 10.36 ± 0.04 at 40°) observed[14] for the formamido group of II ($R^1 = R^2 = Me$) suggested the use of a weaker base for generation of the formamido anion prior to the methylation. Thus, II ($R^1 = R^2 = Me$) was treated with anhydrous K_2CO_3 in DMF at room temperature for 1 hr. When the resulting mixture was methylated as described above, the desired N-methylformamido derivative (III, $R^1 = R^2 = R^3 = Me$) was obtained in 84% yield. Alkylations of II ($R^1 = R^2 = Me$) with EtI and $PhCH_2Br$ and those of II ($R^1 = R^2 = Et$, $R^1 = Et$; $R^2 = PhCH_2$) with the three alkyl halides were also found to proceed equally well under similar reaction conditions to furnish the corresponding N-alkylformamido derivatives (III) [$R^1 = R^2 = Me$; $R^3 = Et$ (mp 95–96°), $R^1 = R^2 = Me$; $R^3 = PhCH_2$ (a glass), $R^1 = R^2 = Et$; $R^3 = Me$ (mp 147–148°),[15] $R^1 = R^2 = R^3 = Et$ (mp 132–133°), $R^1 = R^2 = Et$; $R^3 = PhCH_2$ (mp 69.5–71°), $R^1 = Et$; $R^2 = PhCH_2$; $R^3 = Me$ (mp 82.5–84.5°), $R^1 = R^3 = Et$; $R^2 = PhCH_2$ (mp 102.5–103°), $R^1 = Et$; $R^2 = R^3 = PhCH_2$ (mp 97–98°)] in 83–95% yields. The N-alkylformamido structure of III thus prepared was further supported by the alkaline hydrolysis (1 N aq. NaOH, reflux, 15 min) of III ($R^1 = R^2 = R^3 = Me$ or $R^1 = R^2 = Et$; $R^3 = Me$) to give the known[10] methylamino derivative (V, $R^1 = R^2 = Me$ or Et) (97–99% yield).

Removal of the alkoxyl group from III was then effected by catalytic hydrogenolysis under conditions which we featured[16] in our recent hydrogenolytic cleavage of N′-alkoxy group of a similar amidine system. Hydrogenation of III ($R^1 = R^2 = R^3 = Me$) over Raney Ni in the presence of one molar equivalent of HCl (H_2O, 1 atm, room temp., 3 hr) provided IV·HCl ($R^2 = R^3 = Me$) [mp 278–279° (dec.)] in 66% yield. Similar hydrogenolyses of the other N′-alkoxyamidines (III) described above also produced the corresponding amidines (IV·HCl), which were submitted to the cyclization in the next step without purification.

On treatment with a small amount of Et_3N in boiling EtOH for 30 min (method A), IV·HCl ($R^2 = R^3 = Me$) was found to cyclize to 3,9-dimethyladenine hydrochloride (VII·HCl, $R^2 = R^3 = Me$) (see footnote c in Table I) [89% yield; mp 281–282° (dec.)]. The cyclization also took place smoothly in MeOH (reflux, 7–8 hr) in the presence of ca. 2 molar equivalents of HCl (method B) or $HClO_4$ (method C), giving VII·HCl ($R^2 = R^3 = Me$) (73% yield) or VII·$HClO_4$ ($R^2 = R^3 = Me$) (81% yield) identical with an authentic sample.[10] The other eight amidines (IV·HCl) were likewise cyclized by any one of the three methods to the corresponding 3,9-dialkyladenine salts (VII·HX) (36–86% yields from III), which are listed in Table I together with their UV spectral data.

In an attempt to isolate the free base of 3,9-dimethyladenine (VII, $R^2 = R^3 = Me$), an aqueous solution of VII·HCl ($R^2 = R^3 = Me$) was passed through a column of Amberlite IRA-402 (HCO_3^-). However, the substance isolated from the eluate was the hydrogen carbonate salt (VII·H_2CO_3, $R^2 = R^3 = Me$) [97% yield; mp 161–162° (dec.)], suggesting that the basicity of the free base is considerably high. On the other hand, replacement of the ion-exchange resin by Amberlite CG-400 (OH^-) in the above neutralization resulted in the formation of the methylaminoimidazole (IX, $R^2 = R^3 = Me$), which was characterized as the hydrochloride (IX·HCl, $R^2 = R^3 = Me$) (73% yield; mp 182–183°). Since the same hydrochloride was obtained by a similar treatment of IV·HCl ($R^2 = R^3 = Me$), the above conversion of VII·HCl ($R^2 = R^3 = Me$) into IX ($R^2 = R^3 = Me$) seemed to proceed through the hydrolytic ring

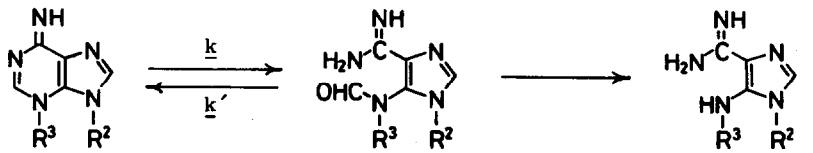
TABLE I. 3,9-Dialkyladenine Salts (VII·HX)

VII·HX			M.p. (°C)[b]	UV Spectra in H_2O[a]			
				pH 1		pH 7	
R^2	R^3	X		λ_{max} (nm)	ε	λ_{max} (nm)	ε
Me	Me	Cl[c]	281–282	270	15700	270	15600
Me	Me	ClO_4[d]	>300	270	15600	270	15400
Me	Et	Cl	251–252	271	15700	271	15600
Me	Et	ClO_4	>300	271	15700	271	15500
Me	$PhCH_2$	ClO_4	>300	272	15900	272	15900
Et	Me	ClO_4[d]	>300	270	16000	270	16000
Et	Et	ClO_4	>300	271	15800	271	15800
Et	$PhCH_2$	ClO_4	226–227	272	16100	272	16000
$PhCH_2$	Me	ClO_4	248–249	271.5	17900	271.5	17900
$PhCH_2$	Et	ClO_4	256–256.5	272	17300	272	17400
$PhCH_2$	$PhCH_2$	ClO_4	206–206.5	273	17800	273	17800

a) Unstable in the alkaline region.
b) With decomposition.
c) The analysis pointed to the formula $C_7H_{10}N_5Cl \cdot 0.4H_2O$.
d) Identified with an authentic specimen (see reference 10).

opening followed by deformylation as delineated in Scheme 2. We found that in 0.1 M aq. $NaHCO_3$ (pH 8.32) at 25° 3,9-dimethyladenine (VII, $R^2 = R^3 = Me$) came to equilibrium with the ring-opened derivative (IV, $R^2 = R^3 = Me$) and the reactions in both directions obeyed pseudo-first-order kinetics ($k = 2.9 \times 10^{-3}$ min^{-1}; $k' = 9.6 \times 10^{-3}$ min^{-1}; $K_{eq} = k/k' = 0.30$) (Scheme 2).[17] For equilibrium between 3-benzyl-9-methyladenine (VII, $R^2 = Me$; $R^3 = PhCH_2$) and IV ($R^2 = Me$; $R^3 = PhCH_2$) were obtained $k = 4.0 \times 10^{-3}$ min^{-1}, $k' = 0.8 \times 10^{-3}$ min^{-1}, and $K_{eq} = k/k' = 5.0$.

Further interest in the ring-opened compounds (IV) stems from the alkaline hydrolysis (1 N aq. NaOH, reflux, 30–60 min) of IV ($R^2 = R^3 = Me$, $R^2 = Me$; $R^3 = Et$, $R^2 = Me$; $R^3 = PhCH_2$, $R^2 = Et$; $R^3 = Me$, $R^2 = R^3 = Et$, $R^2 = R^3 = PhCH_2$), which led to the corresponding carboxamide derivatives (VIII) (44–90% yields from III), identical with authentic samples.[7a,19] The reaction sequence I → II → III



VII IV IX

Scheme 2

→ IV•HCl → VIII (Scheme 1) thus represents an alternative route to the key intermediates utilized in the recent syntheses of 3,9-dialkylhypoxanthines[7a] and 3,9-dialkylguanines.[18,19]

In conclusion, the isolation[20] of 3-methyladenine and 3-ethyladenine from alkylated DNA has stimulated renewed interest in investigations of the synthesis and properties of hitherto unknown 3-methyl- and 3-alkyladenosines (type VII, $R^2 = \beta$-D-ribofuranosyl). It is hoped that the results described above will be of useful help to such investigations.

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