THE CHEMISTRY OF $N^x, N^y, N^z$-TRIMETHYLADENINES AND MORE HIGHLY $N$-METHYLATED ADENINES

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Abstract — Various tri- and poly-$N$-substituted adenines are represented by the corresponding positional isomers of $N^x, N^y, N^z$-trimethyladenine and of more highly $N$-methylated adenines. The chemistry of known isomers of these tri- and poly-$N$-methylated adenines is reviewed with 120 reference citations.

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I. INTRODUCTION

Having a 4-aminopyrimidine ring and an imidazole ring in juxtaposition, the chemical structure of the important fundamental biomolecule adenine (1) ($C_5H_5N_5$) is characterized primarily by the high nitrogen content (51.83%): one exocyclic and four endocyclic nitrogen atoms at the $N^6$, 1-, 3-, 7-, and 9-positions. This permits five kinds of mono-$N$-substitution pattern, 11 kinds of di-$N$-substitution pattern, 15 kinds of tri-$N$-substitution pattern, 15 kinds of tetra-$N$-substitution pattern, 11 kinds of penta-$N$-substitution pattern, five kinds of hexa-$N$-substitution pattern, and one kind of hepta-$N$-substitution pattern for 1 in principle. Indeed, all kinds of the mono- and di-$N$-substitution patterns (with the exception that genuine 1,3-disubstituted adenines still remain unknown), most of the tri-$N$-substitution patterns, and several of the tetra-$N$-substitution patterns have been shown to occur in nature as well as by chemical
Recent review articles by us have treated the chemistry, physicochemical properties, and biological activities of the five positional isomers of N\(_2\)-methyladenine, the prototypes of mono-N-substituted adenines;\(^6\) and of the 11 positional isomers of N\(^2\),N\(^3\)-dimethyladenine, the prototypes of di-N-substituted adenines.\(^7\) Although not all the possible positional isomers of N\(^2\),N\(^2\),N\(^3\)-trimethyladenine and of more highly N-methylated adenines (up to heptamethyladenine) have been known, it is the intention of the present review to treat available data for the known positional isomers in much the same sense as before\(^6\),\(^7\) in order to supplement previous ones\(^1\)–\(^3\) by reorganizing and updating the literature through mid-1998. The positional isomers covered are N\(^6\),N\(^6\),N\(^6\)-trimethyladenine (2),\(^8\) N\(^6\),N\(^6\)-1-trimethyladenine (3), N\(^6\),N\(^6\),3-trimethyladenine (4), N\(^6\),N\(^6\),7-trimethyladenine (5), N\(^6\),N\(^6\),9-trimethyladenine (6), N\(^6\),1,9-trimethyladenine (7), N\(^6\),3,7-trimethyladenine (8), N\(^6\),3,9-trimethyladenine (9), N\(^6\),7,9-trimethyladenine (10),\(^8\) 1,7,9-trimethyladenine (11)\(^8\) (known as the N\(^6\)-methoxy derivative), 3,7,9-trimethyladenine (12)\(^8\) (known as the 8-oxo derivative), N\(^6\),N\(^6\),7-tetramethyladenine (13)\(^8\) (known as the 2-chloro derivative), N\(^6\),N\(^6\),N\(^6\),9-tetramethyladenine (14),\(^8\) N\(^6\),N\(^6\),1,9-tetramethyladenine (15),\(^8\) N\(^6\),N\(^6\),3,7-tetramethyladenine (16),\(^8\) N\(^6\),N\(^6\),3,9-tetramethyladenine (17),\(^8\) and N\(^6\),N\(^6\),7,9-tetramethyladenine (18).\(^8\)

To our certain knowledge, the remaining four isomers of N\(^2\),N\(^3\),N\(^2\)-trimethyladenine [i. e., N\(^6\),1,3-trimethyladenine (19),\(^8\) N\(^6\),1,7-trimethyladenine (20), 1,3,7-trimethyladenine (21)\(^8\) and 1,3,9-trimethyladenine (22)\(^8\)], the remaining nine isomers of tetra-N-methyladenine [i. e., N\(^6\),N\(^6\),N\(^6\),1- (23),\(^8\) N\(^6\),N\(^6\),N\(^6\),3- (24),\(^8\) N\(^6\),N\(^6\),1,3-, N\(^6\),N\(^6\),1,7-, N\(^6\),1,3,7-, N\(^6\),1,3,9-, N\(^6\),1,7,9-, N\(^6\),3,7,9-, and 1,3,7,9-tetramethyladenines], all the 11 isomers of penta-N-methyladenine [i. e., N\(^6\),N\(^6\),N\(^6\),1,3-, N\(^6\),N\(^6\),N\(^6\),1,7-, N\(^6\),N\(^6\),N\(^6\),1,9-, N\(^6\),N\(^6\),N\(^6\),3,7-, N\(^6\),N\(^6\),N\(^6\),3,9-, N\(^6\),N\(^6\),N\(^6\),7,9-, N\(^6\),N\(^6\),N\(^6\),1,3,7-, N\(^6\),N\(^6\),N\(^6\),1,3,9-, N\(^6\),N\(^6\),N\(^6\),1,7,9-, N\(^6\),N\(^6\),N\(^6\),3,7,9-, and N\(^6\),1,3,7,9-pentamethyladenines], all the five isomers of hexa-N-methyladenine [i. e., N\(^6\),N\(^6\),N\(^6\),1,3,7-, N\(^6\),N\(^6\),N\(^6\),1,3,9-, N\(^6\),N\(^6\),N\(^6\),1,7,9-, N\(^6\),N\(^6\),N\(^6\),3,7,9-, and N\(^6\),1,3,7,9-hexamethyladenines], and N\(^6\),N\(^6\),N\(^6\),1,3,7,9-heptamethyladenine have so far been unknown.

II. N\(^6\),N\(^6\),N\(^6\)-TRIMETHYLADENINE

N\(^6\),N\(^6\),N\(^6\)-Trimethyladenine has been synthesized in the salt form [trimethylpurin-6-ylammonium salt (2)] or in the zwitterionic (betaine) form [6-trimethylammoniopurinide (26); N, N, N-trimethyl-1H-purin-6-aminium inner salt (in Chemical Abstracts)]. Horwitz and Vaitkevicius\(^8\) allowed Me\(_3\)N to bubble into a solution of 6-chloropurine (25) in DMF at 0°C and kept the resulting solution at room temperature overnight to obtain 2 (X = Cl) in 80% yield (Scheme 1). Reist et al.\(^10\) secured 2 (X = Cl) in 83% yield from 25 by treatment with anhydrous Me\(_3\)N in a stainless steel bomb at room temperature for 2.5 h. They found that recrystallization of crude 2 (X = Cl) from MeOH gave a crys-
talline 1:1 mixture of 2 (X = Cl) and 2 (X = MeO).\textsuperscript{10} Kiburis and Lister\textsuperscript{11} prepared 2 (X = Cl) in 70% yield from 25 by treating the latter with Me\textsubscript{3}N in a mixture of diglyme [bis(2-methoxyethyl) ether] and DMF at room temperature for \textit{ca}. 2 h. Kießling \textit{et al.}\textsuperscript{12} obtained 2 (X = Cl) or 2 (X = Br) in over 80% yield from 25 or 6-bromopurine, respectively, by treatment with Me\textsubscript{3}N in DMF or in AcNMe\textsubscript{2} at room temperature for several hours. Treatment of 2 (X = Cl) in H\textsubscript{2}O with Dowex 1-X8 (OH\textsuperscript{-}) was reported to produce the zwitterion (26),\textsuperscript{13} which was also obtainable in 50% yield directly from 6-fluoropurine (27) by reaction with Me\textsubscript{3}N in DMF at room temperature for some hours (Scheme 1).\textsuperscript{11} Giner-Sorolla\textsuperscript{14} reported that treatment of 6-chloropurine 3-oxide (28),\textsuperscript{15} prepared from 25 in 88% yield by \textit{m}-CPBA oxidation (Scheme 1), with 25% methanolic Me\textsubscript{3}N at 25°C for 18 h afforded 6-trimethylammoniumpurinide 3-oxide (29) and N\textsubscript{6},N\textsubscript{6}-dimethyladenine 3-oxide (30) in 61% and 12% yields, respectively, and that deoxygenation of 29 with Raney Ni in boiling H\textsubscript{2}O for 30 min gave 26, as identified by means of UV spectral and chromatographic analysis.

![Scheme 1](image_url)

The following may serve to locate papers reporting the physical properties and spectral characteristics of the salt form (2) and the betaine form (26) of N\textsubscript{6},N\textsubscript{6},N\textsubscript{8}-trimethyladenine: the melting point for 2 (X = Cl), mp 191–193°C (decomp),\textsuperscript{11} 191–192°C,\textsuperscript{13a} 189–191°C (decomp),\textsuperscript{9c} 187–189°C,\textsuperscript{16a} 179–180°C,\textsuperscript{9a,12} 179–180°C (decomp),\textsuperscript{9b} or 175–180°C (decomp);\textsuperscript{10} for a 1:1 mixture of 2 (X = Cl) and 2 (X = MeO), mp 165–232°C;\textsuperscript{10} for 2 (X = Br), mp 181°C;\textsuperscript{12} for 26, mp 194°C\textsuperscript{11} or 190–192°C;\textsuperscript{13a,b} for 26-picrate, mp (not particularly specified);\textsuperscript{13a} pK\textsubscript{a} for 2 (X = Cl), 6.85\textsuperscript{16a} or 6.8\textsuperscript{13a,17} or 6.46;\textsuperscript{18} lipophilicity for 2 (X = Cl);\textsuperscript{17} paper chromatography for 2 (X = Cl) and for a 1:1 mixture of 2 (X = Cl) and 2 (X = MeO);\textsuperscript{10} TLC for 2 (X = Cl) and for 2 (X = Br);\textsuperscript{12} column chromatography for 26;\textsuperscript{19} MS for 2 (X = Cl) and for 2 (X = Br);\textsuperscript{12} liquid secondary-ion MS for 2 (X = Cl);\textsuperscript{20} UV for 2 (X =
Cl) in H₂O at various pH's,⁹c,¹⁰,¹²,¹⁶a,¹⁷ for a 1:1 mixture of 2 (X = Cl) and 2 (X = MeO) in H₂O at various pH's,¹⁰ for 2 (X = Br),¹² and for 2⁶ in H₂O at various pH's;¹¹,¹³a IR for 2 (X = Cl),¹¹,¹² for 2 (X = Br),¹² and for 2⁶;¹¹ ¹H NMR for 2 (X = Cl) in D₂O¹¹,¹₆a and in DMSO,²¹ for a 1:1 mixture of 2 (X = Cl) and 2 (X = MeO) in D₂O,¹⁰ and for 2⁶ in D₂O¹³a and in TFA;¹¹ ¹³C NMR for 2 (X = Cl) in DMSO-d₆.²²

As regards the chemical behavior of 2 and 2⁶, Kiburis and Lister¹¹ reported that treatment of 2 (X = Cl) with potassium hydrogen fluoride in 5% aqueous EtOH at 60°C for 3 h or in DMF at 80°C for 2 h furnished 6-fluoropurine (2⁷) in 27% or 35% yield, respectively (Scheme 2), and that 2⁷ was convertible into adenine (1) (in boiling aqueous NH₃ for 1 h or in ethanolic NH₃ at room temperature for 10 d) and into hypoxanthine (in boiling H₂O for 1 h or in 0.1 N aqueous HCl at room temperature for 30 min). Irie et al.²³ prepared ¹⁸F-labeled 6-fluoropurine (3¹) from 2 (X = Cl) in 37.7% radiochemical yield by treatment with anhydrous K¹⁸F in DMF containing 18-crown-6 at 80°C for 30 min. Barlin and Young¹⁶a reported the reaction of 2 (X = Cl) with hot aqueous NaOH (7 x 10⁻² N) for 5 min to produce hypoxanthine, as identified by means of paper chromatography, together with its kinetic results. They also reported that heating 2 (X = Cl) with 0.1 M methanolic MeONa at 50°C for 10 min gave 6-methoxypurine (3²: R = Me) in 91% yield.¹⁶b Burns' group²⁴ synthesized eight 6-alkoxypurines [3²: R = CH₂FCH₂, CF₃CH₂, allyl, (±)-MeCH₂CH(Me), MeCH=CHCH₂, (±)-Me(CH₂)₂CH(Me), Et₂CH, and Me(CH₂)₅] from 2 (X = Cl) by treating with appropriate alcohols and NaOH in THF at room temperature. The use of 2 (X = Cl) as a reactant for similar modification of the 6-substituent was also reported.²⁵

Sublimation of 2⁶ at 185°C and 15 mmHg for 45 min was found to produce N⁶, N⁶,9-trimethyladenine (6) in 49% yield (Scheme 2).²⁶ Heating 2⁶ in the presence of 2,8-dichloro-N⁶, N⁶-dimethyladenine was reported to give a product containing 6 and a certain

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![Scheme 2](image-url)
amount of 2,8-dichloro-N⁶,N⁶,9-trimethyladenine (44), suggesting that migration of a Me group in 26 proceeds inter- rather than intramolecularly. Vieira and Steenken have reported the results of reaction of 2 (X = Cl) with the OH radical in H₂O at pH 6–8 and 20°C. The interactions between lima bean lectin and adenine (1) were examined by using a series of synthetic purine analogues including 2 (with unspecified anion, X⁻), and progressive methylation of the C(6)-NH₂ group was found to give decreasing binding affinity in the order NH₂ > NHMe > NMe₂ > N⁺Me₃. There have been ca. 10 papers dealing with the biological activities of 2 (X = Cl). Merker reported that it was a moderate but transient hypotensive agent in the anesthetized dog and cat. No biological activity with respect to starfish oocyte maturation was found for 2 (X = Cl) by Monsees et al. It had some effect against Ehrlich ascites tumor, transplantable epidermoid carcinoma DC-5, and adenocarcinoma 755 in mice. In humans, objective tumor regressions were also observed with this agent. It had no effect against transplantable sarcoma 180 or leukemia. It (2 with unspecified anion, X⁻) was among a number of 6-mono- and 2,6-disubstituted purines used for prediction of activity against adenocarcinoma CA755 in mice on the basis of quantitative structure–activity relationships of purines. Sidwell et al. reported that 2 (X = Cl) had moderate or questionable anticytomegalovirus activity in vitro. The specificity of rabbit liver aldehyde oxidase (EC 1.2.3.1) toward purine and its derivatives was quantitatively studied, and 2 (with unspecified anion, X⁻) was found to have low substrate efficiency. Inhibition of the following enzymes by 2 (X⁻ = Cl⁻ or unspecified anion) has been reported: cyclin-dependent kinases from a variety of sources; xanthine oxidase; adenine phosphoribosyltransferase from Ehrlich ascites tumor cells. The nonbiological, technical, or engineered material uses of 26 as a chelating agent in the recovery of trace metals such as Co, of 2 (X = Cl) for preparation of jet-printing sheets, and of 2 (X = Cl) as a transparentizing agent for electrophotographic migration imaging members have been applied for patents.

III. N⁶,N⁶,1-TRIMETHYLADENINE

In 1964, Pal and Horton reported that methylation of N⁶,N⁶-dimethyladenine (33) with dimethyl sulfate in a 4:1 mixture of 0.01 M phosphate buffer (pH 7.0) and EtOH at pH 7.0 and room temperature for 3–4 h gave N⁶,N⁶,1-trimethyladenine (3) (22.9% yield), N⁶,N⁶,3-trimethyladenine (4) (66%), and N⁶,N⁶,9-trimethyladenine (6) (8.3%), as shown in Scheme 3. Although they were able to obtain a crystalline picrate from 3, the structure of 3 was inferred only by its sensitivity toward alkali. Townsend et al. synthesized 3 unambiguously by treatment of 6-benzylthio-1-methylpurine (34) with ethanolic Me₂NH. Methylation of 3 with MeI in DMF in a closed vessel at 100°C for 10 min was reported to yield N⁶,N⁶,1,9-tetramethyladeninium iodide (15: X = I).
The following physical properties and spectral characteristics of \( N^6, N^6, 1 \)-trimethyladenine (3) have been reported in the literature: the melting point for the free base (3), mp 199-200°C;\(^{39}\) for the picrate, mp 219°C;\(^{38}\) paper chromatography;\(^{39}\) MS;\(^{41}\) UV in H\(_2\)O at various pH's;\(^{39,42}\) \(^1\)H NMR in DMSO-\(d_6\).\(^{39}\)

\[
\begin{align*}
\text{Scheme 3}
\end{align*}
\]

**IV. \( N^6, N^6, 3 \)-TRIMETHYLADENINE**

As described above in Section III (Scheme 3), \( N^6, N^6, 3 \)-trimethyladenine (4) was the main product from the direct methylation of \( N^6, N^6 \)-dimethyladenine (33) with dimethyl sulfate at pH 7.0.\(^{38}\) An unequivocal route to 4 was developed by Townsend et al.,\(^{39}\) who allowed 3-methyl-6-methylthiopurine (35) to react with 25% aqueous Me\(_2\)NH in MeOH.
(Scheme 4). Bergmann et al.\textsuperscript{43} prepared 4 by similar treatment of 6-chloro-3-methylpurine (36), which was obtainable from 35 by reaction of chlorine in cold MeOH. Separate aminations of 6,8-dichloropurine (37) and 2,6,8-trichloropurine (38) with Me\textsubscript{3}N in 1,2-dimethoxyethane at room temperature for 30 h were reported to produce the corresponding 6-trimethylammoniopurinides (39 and 40) in 58% and 85% yields, respectively.\textsuperscript{26} Sublimation of 39 at 185°C and 15 mmHg for 10 min gave the N\textsuperscript{6},N\textsuperscript{6},3-trimethyl isomer (41) (38% yield) and the N\textsuperscript{6},N\textsuperscript{6},9-trimethyl isomer (43) (38%).\textsuperscript{26} Similar thermal isomerization (at 205°C and 15 mmHg for 45 min) of 40 afforded 2,8-dichloro-N\textsuperscript{6},N\textsuperscript{6},3-trimethyladename (42) (12% yield) and 2,8-dichloro-N\textsuperscript{6},N\textsuperscript{6},9-trimethyladenine (44) (53%).\textsuperscript{26} In addition, treatment of either 8-chloro-N\textsuperscript{6},N\textsuperscript{6}-dimethyladenine or 2,8-dichloro-N\textsuperscript{6},N\textsuperscript{6}-dimethyladenine with dimethyl sulfate in aqueous alkali was reported to give a mixture of the corresponding 3-methyl (41 or 42) and 9-methyl (43 or 44) derivatives in each case.\textsuperscript{26} Catalytic hydrogenolysis of either 41 or 42 in aqueous MeOH containing BaCO\textsubscript{3} over 5% Pd–C catalyst yielded 4, which was found to sublime unchanged.\textsuperscript{26}

![Scheme 5](image)

In an alternative synthesis of 4 (Scheme 5), Itaya \textit{et al.}\textsuperscript{44} methylated N\textsuperscript{6},N\textsuperscript{6}-dimethyladenosine (45) with MeI in AcNMe\textsubscript{2} at 40°C for 7 d and were able to isolate 4 (29% yield) and N\textsuperscript{6},N\textsuperscript{6},3,9-tetramethyladeninium iodide (17: X = I) (6%) from the reaction mixture.
They assumed that 4 had resulted from glycosidic bond cleavage of the primary product (46) by nucleophilic attack of $\Gamma^-$ at the 1'-position; and 17 ($X = I$), from subsequent methylation of 4. Thus, they converted 45 into the tri-O-benzoyl derivative (47) by treatment with benzoyl chloride and pyridine or into the tri-O-benzyl derivative (48) by treatment with benzyl chloride [KOH/dioxane/benzene (91% yield) or NaH/DMF (89% yield)] and methylated either 47 or 48 with MeI in AcNMe$_2$ at 40°C for 240 h or 144 h, respectively, to obtain the corresponding 3-methyl derivative [49 (83% overall yield from 45) or 50 (81% yield from 48)]. Deglycosylation of 49 or 50 was then effected in AcOH at 100°C for 3 h or 30 min, giving 4 (as the picrate) in 37% or 90% yield, respectively. The free base (4) was obtained in 89% yield from 50 by treating the latter with boiling AcOH for 30 min. Later on, Monsees et al. reported that methylation of 45 with MeI in AcNMe$_2$ at 65°C for 24 h afforded 4 in 9.5% yield.

In yet another synthesis of 4, Itaya et al. methylated 33 with MeI in AcNMe$_2$ in the absence of added base at 40°C for 48 h to obtain a 10:1 mixture of the 3- and 9-methyl derivatives, from which 4 (83% yield) and 6 (0.7%) were isolated by chromatographic separation (Scheme 6). On the other hand, treatment of 33 with K$_2$CO$_3$ in boiling AcNMe$_2$ for 10 min and subsequent methylation with MeI (20% excess) in AcNMe$_2$ at room temperature for 4–9 h afforded a 2:7 mixture of 4 and 6, and chromatographic purification of the mixture furnished 4 (14% yield) and 6 (54%).

Muravich-Aleksandr et al. reported that methylation of 4 with MeI in DMF in a closed vessel at 100°C for 10 min or at 20–25°C for 3–5 h gave 17 ($X = I$) in 96% or 77.5% yield, respectively (see Section XVII and Scheme 26), and Itaya et al. methylated a 2:7 mixture of 4 and 6, derived from the above methylation of 33 in the presence of K$_2$CO$_3$, with MeI in AcNMe$_2$ at 40°C for 50 h to obtain 17 ($X = I$) in 95% overall yield from 33 (Scheme 6).

![Scheme 6](image-url)
Condensation of 4 with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 1,2-dichloroethane containing SnCl4 at room temperature for 4 h, followed by treatment of the crude product with NaI in EtOH, was reported to give the 9-ribosyl derivative (49) in 35% yield (Scheme 5).47 Pal and Horton38 reported that Pauly test on 4 was negative and that treatment of 4 with 1 N aqueous NaOH at 100°C for 2–4 h produced 3-methylhypoxanthine (51) and 5-methylaminomidazole-4-carboxamide (52) (Scheme 7), as identified by means of paper chromatography and UV spectral analysis.

Scheme 7

The following physicochemical properties of N6,N6,3-trimethyladenine (4) have been recorded in the literature: the melting point for the free base (4), mp 173–174°C,45 172–173°C,44b 169–170°C,38 or 167–168°C;39 for 4-picrate, mp 196–197°C (with sintering at 189°C)44b or 190°C;38,43 pKₐ 5.8;17,38 lipophilicity,17 paper chromatography;39 MS,17,41 UV in H₂O at various pH's,17,38,39,45,48 in 95% aqueous EtOH,45 or in EtOH;49 IR (KBr);38 ¹H NMR in CDCl₃,45,50,51 in DMSO-d₆17,39,52 (long-range spin–spin coupling of 0.4 Hz over four bonds between the N(3)-Me and the adjacent ring C-H protons52), in TFA,40,51 or in D₂O/D₂SO₄;52 dipole moment, 4.20 ± 0.03 D (determined in benzene at 30.0 ± 0.1°C);49 electrocapillary curve (in 0.1 M Na₂SO₄ and in 0.1 N H₂SO₄);53 activation parameters.51

Scheme 8

The structure of 3-substituted N₆,N₆-dimethyladenine [i.e., the importance of the dipolar iminium form (54) to the possible resonance hybrid [53 ↔ 54 ↔ 55 (Scheme 8)], as suggested51 by nonequivalent N₆-Me₂ signals17,45,50,51 in the ¹H NMR spectrum of the free base of 4] was substantiated by X-ray analysis of 3-(2,6-dichlorobenzyl)-N₆,N₆-dimethyladenine.54
As regards the biological activity of 4, Monsees et al.\textsuperscript{17} reported that this substance was able to induce oocyte maturation in the starfish \textit{Asterias rubens}, but at very high concentrations (EC\textsubscript{50} > 130 \mu M).

V. \textit{N}^6,\textit{N}^6,7-TRIMETHYLADENINE

In 1954, Baker et al.\textsuperscript{55} reported that methylation of \textit{N}^6,\textit{N}^6-dimethyl-2,8-bis(methylthio)adenine (56) with dimethyl sulfate in hot 1 N methanolic MeONa for 15 min furnished \textit{N}^6,\textit{N}^6-\textit{7''}-trimethyl-2,8-bis(methylthio)adenine (57) (27\% yield) and \textit{N}^6,\textit{N}^6,9-trimethyl-2,8-bis(methylthio)adenine (58) (51\%) (Scheme 9). Separate desulfurizations of the two products with Raney Ni produced two isomers described by them\textsuperscript{55} as \textit{N}^6,\textit{N}^6,\textit{7''}-trimethyladenine (5) (50\% yield) and \textit{N}^6,\textit{N}^6,9-trimethyladenine (6) (72\% yield). Later on, Townsend et al.\textsuperscript{39} revealed that the last of these structures had been assigned correctly and the compound was identical with a sample of 6, mp 119–120\degree C, synthesized by an unambiguous route\textsuperscript{56} (see Section VI and Scheme 10), but the structure of the first isomer, mp 168–169\degree C, was in reality \textit{N}^6,\textit{N}^6,3-trimethyladenine (4) since it was identical with an authentic sample prepared from 3-methyl-6-methylthiopurine (35) and Me\textsubscript{2}NH (see Section IV and Scheme 4). It follows that the two products obtained by Baker and co-workers\textsuperscript{55} from 56 by direct methylation were 59 (instead of 57) and 58 and that the desulfurization products were 4 (instead of 5) and 6 (Scheme 9).

![Scheme 9](image)

The unreached isomer \textit{N}^6,\textit{N}^6,7-trimethyladenine (5) was then synthesized by treatment of a pure sample of 6-chloro-7-methylpurine (60)\textsuperscript{57} with 25\% aqueous Me\textsubscript{2}NH.\textsuperscript{39} The following physicochemical data of 5 are found in the literature: the melting point for the free base (5), mp 111–112\degree C;\textsuperscript{39} paper chromatography;\textsuperscript{39} MS;\textsuperscript{41} UV in H\textsubscript{2}O at
various pH's;\textsuperscript{39,42} \textsuperscript{1}H NMR in DMSO-$d_6$\textsuperscript{39} or in D$_2$O.\textsuperscript{58}

VI. $N^6,N^6,9$-TRIMETHYLADENINE

The first synthesis of $N^6,N^6,9$-trimethyladenine (6) was accomplished by Baker and co-workers\textsuperscript{55} through a route starting with methylation of $N^6,N^6$-dimethyl-2,8-bis(methylthio)adenine (56) and proceeding \textit{via} $N^6,N^6,9$-trimethyl-2,8-bis(methylthio)adenine (58), as described above in Section V (Scheme 9).

![Scheme 10]

Treatment of 6-chloro-9-methylpurine (61) with aqueous Me$_2$NH in EtOH\textsuperscript{56} or with 33% ethanolic Me$_2$NH at 20°C for 7 h\textsuperscript{16a} was reported to give 6 in 78% or unspecified yield, respectively (Scheme 10). As described in Section II (Scheme 2), 6 was obtained in 49% yield by sublimation of 6-trimethylammoniopurinide (26) at 185°C and 15 mmHg for 45 min.\textsuperscript{26} Kiburis and Lister\textsuperscript{26} prepared 6 by catalytic hydrogenolysis of 8-chloro-$N^6,N^6,9$-trimethyladenine (43) or 2,8-dichloro-$N^6,N^6,9$-trimethyladenine (44) [derived from 39 or 40, respectively (see Section IV and Scheme 4)] over 5% Pd–C catalyst in aqueous MeOH containing Na$_2$CO$_3$ (Scheme 10). See Sections III (Scheme 3) and IV (Scheme 6) for the methylation of $N^6,N^6$-dimethyladenine (33) to give 6 by the procedure of Pal and Horton\textsuperscript{38} (dimethyl sulfate/0.01 M phosphate buffer (pH 7.0)–EtOH, pH 7.0, rt, 3–4 h; 8.3% yield) and by that of Itaya \textit{et al.}\textsuperscript{45} (MeI/AcNMe$_2$ in the presence or absence of K$_2$CO$_3$; 54% or 0.7% yield, respectively). Bryant and Klein\textsuperscript{59} reported quantitative conversion of either adenine (1) or $N^6$-methyladenine (62) into 6 by methylation with MeI in hot DMSO containing MeONa (Scheme 10). Kelly \textit{et al.} prepared 6 in 36% yield from $N^6,N^6$-dimethyladenine (33) by methylation with MeI under similar reaction conditions.\textsuperscript{60}
Robins’ group\textsuperscript{61} transformed 9-methyladenine (63) into the 6-(1,2,4-triazol-4-yl)purine derivative (65) (85\% yield) by treatment with 1,2-bis[(dimethylamino)methylene]hydrazine dihydrochloride (64·2HCl) in boiling DMF for 66 h and then converted 65 into 6 in 99\% yield by treatment with 40\% aqueous Me\textsubscript{2}NH at room temperature for 1 h (Scheme 11).

![Scheme 11](image)

As regards the chemical behavior of N\textsuperscript{6}, N\textsuperscript{6}, 9-trimethyladenine (6), Muravich-Aleksandr et al.\textsuperscript{40} reported that methylation of 6 with MeI in DMF in a closed vessel at 100°C for 10 min or at 20–25°C for 3–5 h furnished N\textsuperscript{6}, N\textsuperscript{6}, 3,9-tetramethyladeninium iodide (17: X = I) in 89% or 56.5% yield, respectively (see Section XVII and Scheme 26). See also Section IV (Scheme 6) for methylation by Itaya’s group\textsuperscript{46} of a mixture of 6 and N\textsuperscript{6}, N\textsuperscript{6}, 3-trimethyladenine (4) to give 17 (X = I) in 95% overall yield [from N\textsuperscript{6}, N\textsuperscript{6}-dimethyladenine (33)].

![Scheme 12](image)

Kos and van der Plas\textsuperscript{62} reported the reductive removal of the dimethylamino group from 6 to provide 9-methylpurine (66) in 53\% or 55\% yield, which was feasible by treatment with sodium in liquid NH\textsubscript{3} containing diethyl ether for 15 min or 30 min (Scheme 12). Treatment of 6 with m-CPBA in MeOH at 30°C for 48 h was found to produce 9-methylhypoxanthine (67) in 18\% yield, together with 26\% recovery of the
starting material (6).\textsuperscript{63} Reaction of 6 with bromine in 0.5 M AcONa–AcOH buffer (pH 4) at room temperature for 46 h afforded the 8-bromo derivative (68) (68% yield), which was then converted into the 8-oxo derivative (69) in 80% yield by treatment with boiling 1 N aqueous NaOH for 7 h.\textsuperscript{64} The reactions of 6 with the OH radical in H\textsubscript{2}O at pH 6–8 and 20°C\textsuperscript{18,65} and with sulfate radical anion (SO\textsubscript{4}−) in H\textsubscript{2}O at pH 7–8 and 20°C\textsuperscript{65a} have been investigated.

Interactions of 6 with the following substances have been reported: H\textsubscript{2}O (hydration);\textsuperscript{66} each of purine,\textsuperscript{60b,67} 7,9-dimethylguanine, 7-methylguanosine, and 7-methylguanosine 5’-monophosphate in H\textsubscript{2}O at 298.2 K;\textsuperscript{67} 3,5-dichlorophenol in CHCl\textsubscript{3};\textsuperscript{68} each of phenol, 3-bromophenol, 4-bromophenol, 3,4-dichlorophenol, 3,5-dichlorophenol, and 3,4,5-trichlorophenol in 1,2-dichloroethane or in tetrachloroethylene;\textsuperscript{69} 4-bromophenol in CCl\textsubscript{4};\textsuperscript{69} 5,6,8-trideuterio-4-nitroquinoline 1-oxide in DMSO-d\textsubscript{6};\textsuperscript{70} lima bean lectin (see also Section II);\textsuperscript{27} self-association in H\textsubscript{2}O;\textsuperscript{71} [M(dien)(D\textsubscript{2}O)]\textsuperscript{2+} (M = Pt or Pd; dien = diethylenetriamine) or trans-[Pt(NH\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}]\textsuperscript{+} in D\textsubscript{2}O\textsuperscript{71} and reactions of the resulting complex with other nucleobases such as 9-ethylguanine, 9-methyladenine (63), and 1-methylcytosine in D\textsubscript{2}O.\textsuperscript{72}

VII. N\textsuperscript{6},N\textsuperscript{6},9-TRIMETHYLADENINE

In 1973, El’tsov \textit{et al.}\textsuperscript{83} reported that methylation of N\textsuperscript{6},9-dimethyladenine (70) with MeI in DMF in a closed vessel at 100–105°C for 10 min gave a 51:30:19 mixture (94%
yield) of \( N^6,1,9 \)-trimethyladenine hydriodide (7·HI), \( N^6,3,9 \)-trimethyladenine hydriodide (9·HI), and \( N^6,7,9 \)-trimethyladeninium iodide (10: \( X = I \)), from which they were able to isolate pure samples of the three products (Scheme 13). The deuterated products (71–73) were obtained similarly by using CD\(_3\)I instead of MeI.\(^{83}\) Alternatively, 7·HI was synthesized from \( N^6,1 \)-dimethyladenine (74) in 72.5% yield by methylation with MeI in DMF in a closed vessel at 100°C for 10 min.\(^{83}\) Fujii's group\(^ {84} \) found that reaction of 70 with MeI in AcNMe\(_2\) at 40°C for 6 h produced 7·HI [isolated as the perchlorate salt (7·HClO\(_4\)) in 11% yield] and 9·HI (17%). Direct methylation of \( N^6 \)-methyladenine (62) with an excess of MeI in AcNMe\(_2\) at 38–42°C for 6 h was found to provide 7 (isolated as 7·HClO\(_4\) in 0.3% yield), together with \( N^6,3 \)-dimethyladenine (75) (82%), \( N^6,9 \)-dimethyladenine (70) (1.3%), and \( N^6,3,7 \)-trimethyladenine (8) (1.8%) (Scheme 14).\(^{84}\) The \( N^6,1,9 \)-trimethyl (7·HI), \( N^6,3,9 \)-trimethyl (9·HI), and \( N^6,3,7 \)-trimethyl (8·HI) isomers were the products (78–90% or 41% total yield) from the thermal reaction of the \( N^6,7,9 \)-trimethyl isomer (10: \( X = I \)) at 220°C for 7–30 min or in boiling nitrobenzene for 30 min.\(^{83}\)

\[ \text{Scheme 13} \]

\[ \text{Scheme 14} \]
Heating 7-HI in boiling nitrobenzene for 30 min was reported to give a 18.5:24.0:57.5 mixture (30% yield) of 9-HI, 8-HI, and 7-HI.\textsuperscript{83} The polarographic reduction of 7-HI has been investigated by Timofeeva \textit{et al.}\textsuperscript{85} See Section IX (Scheme 16) for the synthesis of the 8-oxo derivative (83) of 7.

The following physicochemical properties of \textit{N}^6,1,9-trimethyladenine (7) are recorded in the literature: the melting points for the free base (7), mp 158°C;\textsuperscript{83} for the hydriodide (7-HI), mp 249–251°C;\textsuperscript{83} for the perchlorate (7-HClO$_4$), mp 209–210°C\textsuperscript{84} or 208–209°C;\textsuperscript{83} pK\textsubscript{a} (for 7-HI) 10.00 ± 0.04;\textsuperscript{83} paper chromatography for 7-HI;\textsuperscript{83} UV for 7-HI in H$_2$O,\textsuperscript{83} for 7-HClO$_4$ in H$_2$O (at pH 1, 7, and 13) and in 95% aqueous EtOH;\textsuperscript{84} $^1$H NMR for 7 in CDCl$_3$;\textsuperscript{83} electrocapillary curve for 7-HClO$_4$ (in 0.1 M Na$_2$SO$_4$ and in 0.1 N H$_2$SO$_4$).\textsuperscript{53}

\section*{VIII. \textit{N}^6,3,7-TRIMETHYLADENINE}

El'tsov \textit{et al.}\textsuperscript{83} reported that methylation of \textit{N}^6,3-dimethyladenine (75) with MeI in DMF in a closed vessel at 100°C for 10 min provided \textit{N}^6,3,7-trimethyladenine hydriodide (8-HI) (64% yield) and \textit{N}^6,3,9-trimethyladenine hydriodide (9-HI) (16%) (Scheme 15). Alternatively, they synthesized 8-HI in 80% yield from 3,7-dimethyl-6-methylthiopurinum iodide (77) by treatment in acetonitrile with a 17% solution of MeNH$_2$ in acetonitrile in a closed vessel at 80–100°C for 30 min.\textsuperscript{83} The N(7)-CD$_3$ species (76-HI) was also prepared from 7-deuteriomethyl-3-methyl-6-methylthiopurinum iodide (78) in a similar manner.\textsuperscript{83} Fujii's group\textsuperscript{84} found that methylation of 75 with MeI in AcNMe$_2$ at 38–40°C for 6 h gave 8-HI [isolated as the perchlorate (8-HClO$_4$) in 29% yield] and 9-HI (15%), the results being in general agreement with the above results\textsuperscript{83} obtained by the Russian research group under slightly different conditions, and that 8-HI [isolated as the perchlorate (8-HClO$_4$) in 1.8% yield] was among the four products from the reaction of \textit{N}^6-methyladenine (62) with MeI in AcNMe$_2$ at 38–42°C for 6 h (see Section VII and Scheme 14). The \textit{N}^6,3,7-trimethyl compound (8-HI) was among the products from the methylation of 3-methyladenine or its hydriodide with MeI in DMF at 100°C or 150°C, respectively, for 4 h.\textsuperscript{86}
When heated in boiling nitrobenzene for 30 min or 1 h, 8-HI was recovered in 83.5% yield or furnished a 93.8 : 6.2 mixture of 8-HI and N⁶,1,9-trimethyl isomer (7-HI) in 52.2% yield, respectively. Timofeeva et al. have reported the results of their study on the polarographic reduction of 8-HI.

The following physical properties and spectral characteristics of N⁶,3,7-trimethyladenine salt (8-HX) have been reported: the melting point for the hydriodide (8-HI), mp 256–257°C; for the perchlorate (8-HClO₄), mp 195–196°C or 191–193°C; pKᵣ (for 8-HI) ca. 11.60; paper chromatography for 8-HI; MS for 8-HClO₄ and 76; UV for 8-HI in H₂O; for 8-HClO₄ in H₂O at various pH's and in 95% aqueous EtOH; ¹H NMR for 8-HI in TFA.

IX. N⁶,3,9-TRIMETHYLADENINE

As described above in Section VII, N⁶,3,9-trimethyladenine hydriodide (9-HI) was synthesized as one of the products from methylation of N⁶,9-dimethyladenine (70) with MeI in DMF at 100–105°C for 10 min or in AcNMe₂ at 40°C for 6 h. It was also obtainable from N⁶,3-dimethyladenine (75) by methylation with MeI in DMF at 100°C for 10 min or in AcNMe₂ at 38–40°C for 6 h (see Section VIII and Scheme 15). See also Section VII for the formation of 9-HI in thermal isomerization of N⁶,1,9-trimethyladenine hydriodide (7-HI) or the N⁶,7,9-trimethyl isomer (10-HI) and for the preparation of the N(3)-CD₃ species (72) of 9-HI from 70.

![Scheme 16](image)
Heating 9·HI in boiling nitrobenzene for 30 min was reported to give a 53:25:22 mixture (30–40% yield) of 7·HI, 8·HI, and 9·HI. The polarographic reduction of 9·HI has been investigated by Timofeeva et al.

The following physicochemical data of N6,3,9-trimethyladenine hydriodide (9·HI) are found in the literature: the melting point, mp 262–263°C (decomp) or 261–262°C; pKa 11.00 ± 0.04; paper chromatography; UV in H2O or in H2O at various pH's and in 95% aqueous EtOH; 1H NMR in TFA. N6,3,9-Trimethyladenine (9) occurs in nature as the 8-oxo derivative [3,6,7,9-tetrahydro-3,9-dimethyl-6-(methylimino)-8-oxopurin-7-ide (82) (caissarone)], a novel 8-oxopurine isolated by Zelnik et al. in the form of the hydrochloride salt (81) from the sea anemone Bunodosoma caissarum Correa 1964 (Anthozoa, Actiniaria). The structure of caissarone hydrochloride (81) was established on the basis of spectroscopic measurements and an X-ray crystallographic analysis.

The first synthesis of 81, achieved by Fujii's group, started with methylation of N6,9-dimethyl-8-oxoadenine (79) with MeI in AcNMe2 at 38–43°C for 72 h to give the 3-methylated product [caissarone hydriodide (80)] (57% yield) and the 1-methylated product (83) (15%) (Scheme 16). Treatment of 80 with Amberlite IRA-402 (Cl−) in H2O provided the hydrochloride salt (81) (98% yield), which was identical with a natural sample of caissarone hydrochloride. Furthermore, the synthetic 81 was reduced with NaBH4 in MeOH at room temperature for 21.5 h, and the resulting 1,2-dihydro derivative was isolated in the form of the picrate (84) (74% yield), which proved identical with that prepared from natural 81 in a similar manner. In addition, catalytic hydrogena-
tion of 81 [20% Pd(OH)$_2$-C/H$_2$, 50% (v/v) aqueous AcOH, 1 atm, 60–70°C, 6 h] produced the monocyclic amidine salt (85) in 77% yield, and treatment of 81 with Amberlite IRA-402 (HCO$_3^-$) in H$_2$O furnished the free base (82) of caissarone.$^{64}$ An alternative synthesis of 82 was accomplished via a route starting from N$^6$-3-dimethyladenine (75) and proceeding through the N(7)-oxide (86), the 7-methoxy compound (87), the 8-oxo compound (88), and caissarone hydriodide (80), as delineated in Scheme 17.$^{90}$

**X. N$^6$7,9-TRIMETHYLADENINE**

As described above in Section VII (Scheme 13), El’tsov et al.$^{83}$ obtained N$^6$7,9-trimethyladeninium iodide (10: X = I) as one of the products from methylation of N$^6$9-dimethyladenine (70) with MeI in DMF at 100–105°C for 10 min. Alternatively, treatment of 6-chloro-7,9-dimethylpurinium perchlorate (90) with a solution of MeNH$_2$ in acetonitrile for 10–15 min provided 10 (X = ClO$_4$) in 80% yield.$^{83}$ Conversion of 10 (X = ClO$_4$) into 10 (X = I) through the dihydro derivative (92) and direct reversion of 10 (X = I) to 10 (X = ClO$_4$) were also feasible, as shown in Scheme 18.$^{83}$

![Scheme 18](image)

In 1965, Brown and Jacobsen$^{91}$ reported that methylation of 5-formamido-4,6-bis(methylamino)pyrimidine (89) with MeI in MeOH at 100°C for 2 h$^{92}$ or methylation of N$^6$9-dimethyladenine (70) with MeI at 140°C for 3 h gave a single product (mp 260–261°C), to which they assigned the structure of N$^6$7,9-trimethyladeninium iodide (10: X = I). However, this product was not identical with a sample of 10 (X = I) obtained by the Russian workers; it had the properties and constants corresponding to N$^6$3,9-trimethylade-
nine hydriodide (9·HI). Yamauchi et al. isolated the ring-opened derivative (91) of 10 in 1% yield from the reaction mixture obtained by methylation of adenine (1) with trimethyl phosphate in H2O at pH 10–11 and 60°C for 24 h. See Section VII for the thermal isomerization of 10 (X = I).

The following physicochemical properties of N6,7,9-trimethyladeninium salt (10) are reported in the literature: the melting point for 10 (X = I), mp 198–200°C; for [10 (X = I)]·HI, mp 245–247°C (decomp); for 10 (X = ClO4), mp 139–141°C; paper chromatography for 10 (X = I); UV for 10 (X = I) in H2O; for 10 (X = ClO4) in H2O; 1H NMR for 10 (X = I) in TFA; electrocapillary curve for 10 (X = ClO4); polarography for 10 (X = ClO4).

The 8-oxo derivative (93) of 10 was synthesized from N6,9-dimethyl-8-oxoadenine (79) in 79% yield by methylation with MeI in DMF containing K2CO3 at room temperature for 3 h (Scheme 19). On treatment with 10% ethanolic HCl, 93 afforded the hydrochloride (93·HCl) in 95% yield. See Section VII (Scheme 13) for the preparation of the N(7)-CD3 species (71) of 10 (X = I) from N6,9-dimethyladenine (70).

XI. 1,7,9-TRIMETHYLADENINE

1,7,9-Trimethyladenine (11) has so far been known only as the N6-methoxy derivative.

Fujii's group was able to prepare N6-methoxy-7,9-dimethyladeninium iodide (94: X = I) in 59% yield from N6-methoxy-9-methyladenine by methylation with MeI in AcNMe2 at 30°C for 7 h or in 36% yield from N6-methoxy-7-methyladenine by methylation with
MeI in AcNMe₂ at 40°C for 2 h. Treatment of 94 (X = I) with DBU in boiling EtOH gave the betaine (95) (Scheme 20), and methylation of 95 with MeI in AcNMe₂ at room temperature for 3.5 h yielded N⁶-methoxy-1,7,9-trimethyladeninium iodide (96: X = I) [56% overall yield from 94 (X = I)], mp 230–231°C (decomp); UV \( \lambda_{\text{max}}^{\text{aq. EtOH}} \) 294 nm (ε 8000); \( \lambda_{\text{max}}^{\text{H₂O}} \) (pH 1) 226 (20500), 289 (8800); \( \lambda_{\text{max}}^{\text{H₂O}} \) (pH 7) 226 (20300), 289 (8800); \( \lambda_{\text{max}}^{\text{H₂O}} \) (pH 13) unstable; \(^1\)H NMR (DMSO-\( d_6 \)) δ: 3.38 [3H, s, N(1)-Me], 3.78 [3H, s, OMe or N(9)-Me], 3.85 [3H, s, N(9)-Me or OMe], 3.97 [3H, s, N(7)-Me], 8.29 [1H, s, C(2)-H], 9.37 [1H, s, C(8)-H].

Methylation of N⁶-methoxy-1,9-dimethyladenine (97), prepared from the corresponding perchlorate salt (97·HClO₄) by treatment with Amberlite IRA-402 (Cl⁻) in H₂O, with MeI in AcNMe₂ at room temperature for 3 h also furnished 96 (X = I) in 92% overall yield (from 97·HClO₄).

Treatment of 96 (X = I) with NaClO₄ in hot H₂O afforded the perchlorate [96 (X = ClO₄)l] (89% yield), mp 207–208°C; UV \( \lambda_{\text{max}}^{\text{aq. EtOH}} \) 233 nm (ε 7400), 294 (7900); \( \lambda_{\text{max}}^{\text{H₂O}} \) (pH 1) 229 (7100), 289 (8900); \( \lambda_{\text{max}}^{\text{H₂O}} \) (pH 7) 229 (7000), 289 (8800); \( \lambda_{\text{max}}^{\text{H₂O}} \) (pH 13) unstable; \(^1\)H NMR (DMSO-\( d_6 \)) δ: 3.38 [3H, s, N(1)-Me], 3.77 [3H, s, OMe or N(9)-Me], 3.85 [3H, s, N(9)-Me or OMe], 3.97 [3H, s, N(7)-Me], 8.27 [1H, s, C(2)-H], 9.34 [1H, s, C(8)-H].

XII. 3,7,9-TRIMETHYLADENINE

Up to now, 3,7,9-trimethyladenine (12) is known only as the 8-oxo derivative (100).

\[
\begin{align*}
\begin{array}{c}
\text{NH}_2 \\
\text{Me}
\end{array} \\
\begin{array}{c}
\text{OMe}
\end{array}
\text{Me}
\rightarrow \\
\begin{array}{c}
\text{NH} \\
\text{Me}
\end{array} \\
\begin{array}{c}
\text{OMe} \cdot \text{HCl}
\end{array}
\end{align*}
\]

Scheme 21

Methylation of 8-methoxy-3-methyladenine (98) with MeI in AcNMe₂ at room temperature for 6 h gave, after conversion of the products into the hydrochloride salts followed by hydrolysis in boiling 1 N aqueous HCl for 2 h, 3,7-dimethyl-8-oxoadenine (99) (51%
yield) and 3,7,9-trimethyl-8-oxoadenine hydrochloride (100·HCl) (22%) (Scheme 21). In addition, methylation of 98 with MeI in AcNMe2 at 30°C for 6 h, but without recourse to acid hydrolysis for product isolation, afforded 8-methoxy-3,7-dimethyladenine hydroiodide (101) (29% yield), 99 (23%), 8-methoxy-3,9-dimethyladenine hydroiodide (102) (12%), and 100·HI [isolated as the hydrochloride (100·HCl) in 11% yield]. Methylation of 99 with MeI in AcNMe2 at 30°C for 24 h and treatment of the product with Amberlite IRA-402 (Cl-) in H2O also produced 100·HCl in 77% yield.

An analytical sample of 100·HCl·H2O was reported to have the following physicochemical properties: mp 253–254°C (decomp); UV $\lambda_{\text{max}}^{\text{aq. EtOH}}$ 226 nm (ε 19300), 298 (18600); $\lambda_{\text{max}}^{\text{H2O}}$ (pH 1) 224 (20100), 294 (19300); $\lambda_{\text{max}}^{\text{H2O}}$ (pH 7) 224 (20300), 294 (19300); $\lambda_{\text{max}}^{\text{H2O}}$ (pH 13) unstable; IR $\nu_{\text{max}}$ cm$^{-1}$: 3339, 3106 (NH), 1725 (C=O), 1669 (C=N); $^1$H NMR (DMSO-$d_6$) δ: 3.57 [3H, s, N(7)-Me], 3.66 [3H, s, N(9)-Me], 4.13 [3H, s, N(3)-Me], 8.27 (2H, br, NH$_2$), 8.50 [1H, s, C(2)-H].

XIII. N$^6$,N$^6$,N$^6$,7-TETRAMETHYLADENINE

So far, N$^6$,N$^6$,N$^6$,7-tetramethyladenine (13)$^8$ has been known only as the 2-chloro derivative (104). Kiburis and Lister$^{11}$ reported that treatment of 2,6-dichloro-7-methylpurine (103) with Me$_3$N in DMF at room temperature for 30 min produced 2-chloro-7-methylpurin-6-yltrimethylammonium chloride (104) [mp 178–180°C for 104·H2O; UV $\lambda_{\text{max}}^{\text{H2O}}$ (pH 1) 284 nm (ε 6300); $\lambda_{\text{max}}^{\text{H2O}}$ (pH 7) 284 (6300); $^1$H NMR (D$_2$O) δ: 3.85 (Me$_3$N$^+$), 4.34 [N(7)-Me], 8.89 [C(8)-H] in 82% yield (Scheme 22).

[Scheme 22]

On treatment with a 4% solution of potassium hydrogen fluoride in 50% aqueous EtOH at 0°C for 2 h, 104 gave 2-chloro-6-fluoro-7-methylpurine (105) (88%) yield, which was then led to 6-fluoro-7-methylpurine (106) in 59% yield by hydrogenolysis using 5% Pd–C catalyst and hydrogen in MeOH containing a suspension of BaCO$_3$ in H$_2$O.$^{11}$

XIV. N$^6$,N$^6$,N$^6$,9-TETRAMETHYLADENINE

Barlin and Young$^{16}$ synthesized 9-methylpurin-6-yltrimethylammonium chloride (14: X = Cl) from 6-chloro-9-methylpurine (61) by treatment with Me$_3$N in benzene at room temperature for 24 h (Scheme 23), and Kiburis and Lister$^{11}$ employed slightly different
reaction conditions (Me$_3$N/diglyme, rt, 2 h) to obtain 14 (X = Cl) in 78% yield.

\[
\begin{align*}
\text{Me$_3$N/diglyme, 26°C, 24 h} & \rightarrow 14 (X = Cl) \rightarrow 67
\end{align*}
\]

\[
\begin{align*}
\text{Me$_3$N/benzene, 26°C, 24 h} & \rightarrow 14 (X = Cl) \rightarrow 67
\end{align*}
\]

\[
\begin{align*}
0.5 \text{ M ethanolic EtONa} & \rightarrow 77°C, 15 \text{ min (64% yield)}
\end{align*}
\]

\[
\begin{align*}
\text{KF/ HF} & \rightarrow \text{EtOH or MeCN}
\end{align*}
\]

\[
\begin{align*}
\text{an N$_2$-atom molecule} & \rightarrow \text{NaCN/DMF, 50°C, 2 h}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 23}
\end{align*}
\]

On warming in aqueous NaOH (3.5 \times 10^{-2} M), 14 (X = Cl) gave 9-methylhypoxanthine (67), and a kinetic study was made of this reaction.$^{16a}$ Separate treatments of 14 (X = Cl) with 0.5 M ethanolic EtONa (77°C, 15 min), potassium hydrogen fluoride (in EtOH, 50°C, 2 h), aqueous NH$_3$ (d 0.91)–NH$_4$Cl (50°C, 3 h), PrNH$_2$ (in a sealed tube, 50°C, 3 h), 49% hydrazine hydrate (20°C, 15 min), and NaCN (in DMF, 50°C, 2 h) afforded 6-ethoxy-9-methylpurine (107) (64% yield), 6-fluoro-9-methylpurine (108) (in unspecified yield), 9-methyladenine (63) (67%), 9-methyl-N$^6$-propyladenine (109) (isolated as the picrate in 68% yield), 6-hydrazino-9-methylpurine (110) (33%), and 9-methylpurine-6-carbonitrile (111) (in unspecified yield), respectively (Scheme 23).$^{16b}$ Treatment of 14 (X = Cl) with potassium hydrogen fluoride in acetonitrile at 50–55°C for 5 h was reported to produce 108 in 37% yield.$^{11}$ The hydrated derivative of 14 (X = Cl), containing 2.5 molar equiv. of H$_2$O, has been found to be unstable and is slowly degraded to N$^6$,N$^6$,9-trimethyladenine (6) at room temperature.$^{11}$

The following physicochemical properties of 14 (X = Cl) have been reported in the literature. For [14 (X = Cl)–1.5H$_2$O]$^{16a}$ mp 161–162°C; UV in H$_2$O at pH 4.0; $^1$H NMR in D$_2$O. For [14 (X = Cl)–2.5H$_2$O]$^{11}$ mp 165°C; UV in H$_2$O at pH 1 and 7; IR; $^1$H NMR in D$_2$O and in DMSO-$_d_6$.

**XV. N$^6$,N$^6$,1,9-TETRAMETHYLADENINE**

Muravich-Aleksandr $et$ $al.$$^{40}$ synthesized N$^6$,N$^6$,1,9-tetramethyladeninium iodide (15: X
Their previous description that 15 (X = I) was obtainable from N6,N6,7,9-tetramethyladeninium iodide (18: X = I) by thermal isomerization or from N6,N6,9-trimethyladenine (6) by methylation with MeI turned out to be erroneous.

On heating at 215–220°C for 5–10 min, 15 (X = I) isomerized to give the N6,N6,3,9-tetramethyl compound [17 (X = I)] in 61% yield.40

XVI. N6,N6,3,7-TETRAMETHYLADENINE

N6,N6,3,7-Tetramethyladeninium iodide (16: X = I) was synthesized from 3,7-dimethyl-6-methylthiopurinium iodide (77) and Me2NH (Scheme 25),40,98 as in the case of the reaction of 77 with MeNH2 to give N6,3,7-trimethyladenine hydriodide (8·HI) (Section VIII and Scheme 15).

Isomerization of 16 (X = I) at 215–220°C for 5–10 min or in boiling nitrobenzene for 30 min produced the N6,N6,3,9-tetramethyl isomer (17: X = I) in 60% or 10% yield, respectively.40

The following physical properties and spectral characteristics of 16 have been recorded in the literature: the melting point for 16 (X = I), mp 195–197°C;40 for 16 (X = ClO4), mp 144–145°C;40 paper chromatography for 16 (X = I) and for 16 (X = ClO4);40 UV in H2O
for 16 (X = I) and for 16 (X = ClO₄);¹⁰¹ ¹H NMR for 16 (X = I) in TFA;¹⁰¹ electrocapillary curve for 16 (X = ClO₄);¹⁵³ polarography for 16 (X = ClO₄).⁸⁵

XVII. N⁶,N⁶,3,9-TETRAMETHYLADENINE

As described above in Sections IV and VI, preparation of N⁶,N⁶,3,9-tetramethyladeninium iodide (17: X = I) from either N⁶,N⁶,3-trimethyladenine (4) or N⁶,N⁶,9-trimethyladenine (6) by methylation with MeI in DMF⁴⁰ (Scheme 26) or from a 2:7 mixture of 4 and 6 by methylation with MeI in AcNMe₂ (Scheme 6)⁴⁶ represents the essentially reciprocal directivity in alkylation of N⁶,N⁶,3-trialkyladenines⁴⁶ and N⁶,N⁶,9-trialkyladenines.⁴⁶,⁹⁹,¹⁰⁰ See also Section IV (Scheme 5) for the methylation of N⁶,N⁶-dimethyladenosine (45) to give rise to 17 (X = I) as a by-product. Formations of 17 (X = I) from N⁶,N⁶,1,9-tetramethyladeninium iodide (15: X = I) (Section XV and Scheme 24) and from the N⁶,N⁶,3,7-tetramethyl isomer (16: X = I) (Section XVI and Scheme 25) are described above and that from the N⁶,N⁶,7,9-tetramethyl isomer (18: X = I) will be mentioned below (Section XVIII).

![Scheme 26](image)

The following physicochemical properties of 17 (X = I) are reported: mp 335-345°C⁴⁰ or >300°C;⁴⁶ paper chromatography;⁴⁰ UV in H₂O,⁴⁰ in H₂O at pH 1 and 7;⁴⁶ and in 95% aqueous EtOH;⁴⁶ ¹H NMR in DMSO-d₆⁴⁶ and in TFA;¹⁰¹ electrocapillary curve for 17 (X = ClO₄);¹⁵³ polarography.⁸⁵

As regards the chemical behavior of 17 (X = I), it demethylated to give N⁶,N⁶,9-trimethyladenine (6) in 23.4% yield when heated in boiling nitrobenzene for 30 min.⁴⁰ Itaya’s group¹⁰¹ reported that treatment of 17 (X = I) in boiling 1 N aqueous NaOH for 15 min furnished 1-methyl-5-(methylamino)imidazole-4-carboxamide (112) in 90% yield (Scheme 26) and that this hydrolysis proceeded more rapidly than that⁹⁹ of the N⁶,N⁶-
diethyl analogue to give the same carboxamide (112). This carboxamide (112) is useful as a starting material for the syntheses of 3,9-dimethylpurines, such as 3,9-dimethylguanine (114),\textsuperscript{102} 3,9-dimethylxanthine (115),\textsuperscript{102} 3,9-dimethylhypoxanthine (116),\textsuperscript{103} and 3,9-dimethylisoguanine (117).\textsuperscript{102c,104}

\begin{center}
\begin{tabular}{ccc}
\includegraphics[width=2cm]{114} & \includegraphics[width=2cm]{115} & \includegraphics[width=2cm]{116} \\
114 & 115 & 116
\end{tabular}
\end{center}

The 8-oxo derivative of 17 corresponds to \(N^6\)-methylcaissarone salt, and it was synthesized in the form of the hydrochloride (113) in 44\% yield from \(N^6,N^6,9\)-trimethyl-8-oxoadenine (69) (see Section VI and Scheme 12) by methylation with MeI in AcNMMe\(_2\) at 40–43°C for 216 h followed by treatment of the resulting product with Amberlite IRA-402 (Cl\(^-\)) in H\(_2\)O.\textsuperscript{64}

**XVIII. \(N^6,N^6,7,9\)-TETRAMETHYLADENINE**

The synthesis of \(N^6,N^6,7,9\)-tetramethyladeninium perchlorate (18; \(X = \text{ClO}_4\)) from 6-chloro-7,9-dimethylpurinium perchlorate (90) by amination with Me\(_2\)NH, reduction of 18 (\(X = \text{ClO}_4\)) with NaBH\(_4\) to give the dihydro derivative (118), and oxidation of 118 with iodine (Scheme 27) were effected\textsuperscript{98} as in the cases of the \(N^6,7,9\)-trimethyl series (10 and 92) (Section X and Scheme 18).

\begin{center}
\begin{tabular}{c}
\includegraphics[width=4cm]{90} \\
90
\end{tabular}
\begin{tabular}{cc}
\includegraphics[width=4cm]{18} & \includegraphics[width=4cm]{118} \\
18 & 118
\end{tabular}
\end{center}

**Scheme 27**

When heated at 215–220°C for 5–10 min or in boiling nitrobenzene for 30 min, 18 (\(X = \text{I}\)) isomerized to afford the \(N^6,N^6,3,9\)-tetramethyl compound (17; \(X = \text{I}\)) in 66\% or 30\% yield, respectively.\textsuperscript{40}

The following physicochemical properties of 18 are recorded in the literature: the melting point for 18 (\(X = \text{I}\)), mp 168–170°C\textsuperscript{98} or 167–170°C (melted and resolidified);\textsuperscript{40} for 18 (\(X = \text{ClO}_4\)), mp 146–148°C;\textsuperscript{98} paper chromatography for 18 (\(X = \text{I}\));\textsuperscript{40} UV for 18 (\(X = \text{I}\)) in H\(_2\)O;\textsuperscript{40,98} \(1\)H NMR for 18 (\(X = \text{I}\));\textsuperscript{40,98} polarography for 18 (\(X = \text{ClO}_4\)).\textsuperscript{85,94,95}
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92. Methylation of 89 with MeI at 140°C for 3 h has been reported to yield a product (mp 320°C), which allegedly has the N6,7,9-tetramethyladeninium iodide structure.91


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