4,6-Dimethyl-5-phenyl-3-cyano-2(1)-pyridone (29).—To a solution of 3-phenyl-2,4-pentanedione[23] in anhydrous ethanol was added anhydrous liquid ammonia until the flask remained cold. The resulting slurry was concentrated, cooled, and filtered, affording 70% of the imine.[24]

An equimolar mixture of this imine and cyanoacetamide was heated at 150° for 2 hr. The resulting solid was cooled and recrystallized from glacial acetic acid to afford, after washing with ether, 50% of 4,6-dimethyl-4-phenyl-3-cyano-2(1)-pyridone (29), m.p. 354–356°.[25] The infrared spectrum showed strong absorption at 6.01, 6.21, and 6.50 μ characteristic of a pyridone and absorption at 4.50 μ for CN. The ultraviolet spectrum exhibited maxima at 337 (log ε 4.01) and 242 (log ε 4.01) mμ.

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.88; H, 5.45; N, 12.50.

In an earlier attempt to prepare 29, 3-phenyl-2,4-pentanedione was converted to its salt by aqueous sodium hydroxide, treated with cyanoacetamide, and heated on a steam bath for 2 hr. The resulting slurry was cooled, acidified with acetic acid, and filtered, and the solid was washed thoroughly with water. When a sample of the solid was ignited, a basic residue was left, and an infrared spectrum indicated that the salt of pyridone 29 was present. A residue was no longer obtained on ignition only after several recrystallizations of the solid from acetic acid. Attempts to liberate neutral pyridone 29 by single treatments of the salt with hot, aqueous mineral acids, with hot, concentrated sulfuric acid, and with ammonium chloride in liquid ammonia failed.

Alkylation of Pyridone 29.—To a solution of 0.025 mole of potassium amide in liquid ammonia was added 2.0 g. (0.008 mole) of 29. After 1 hr. 2.7 g. (0.017 mole) of benzyl chloride in 20 ml. of ether was added. When the ammonia had evaporated, ether and cold water were added. The ether layer was dried and evaporated, a residue of 0.65 g. (40%) of stilbene was recovered (identified by mixture melting point with an authentic sample). The aqueous layer (actually a slurry of solid and liquid) was cooled, acidified with 6 *M* hydrochloric acid, and filtered; the product, washed with water and dried, weighed 2.1 g. and left a residue on ignition. An n.m.r. spectrum of this solid indicated that it contained mono- and dibenzylation product in approximately 3:1 ratio (also a very small amount of starting material).

(23) C. R. Hauser and R. M. Manyik, *J. Org. Chem.*, **18**, 588 (1953).
(24) See ref. 15.
(25) This compound was quite insoluble in ethanol, acetone, and water.

Site of Alkylation of N^6,N^6-Dialkyl-9-Substituted Adenines. Synthesis and Alkaline Degradation of 6-Diethylamino-3,9-dimethylpurinium Iodide

JOSEPH W. MARSICO AND LEON GOLDMAN

The Organic Chemical Research Section, Lederle Laboratories, Division of American Cyanamid Company, Pearl River, New York

Received May 5, 1965

N^6,N^6-Diethyl-9-methyladenine (1) was methylated with methyl iodide in ethanol to give 6-diethylamino-3,9-dimethylpurinium iodide (2). Alkaline degradation of 2 at room temperature afforded 1-methyl-5-methylamino-4-(N,N-diethyl)imidazolecarboxamidine hydriodide (6), whereas, at 100°, the degradation proceeded further to produce 1-methyl-5-methylamino-4-imidazolecarbonitrile (5) and then 1-methyl-5-methylamino-4-imidazolecarboxamide (4). The degradation product 4 was synthesized by formylation of 5-amino-1-methyl-4-imidazolecarboxamide (7) and subsequent selective reduction of the formamido group of 8 with lithium aluminum hydride.

Alkylation of purine bases of nucleic acid and their nucleosides has been studied extensively in recent years, both because of intrinsic chemical interest, and to provide information relative to certain biochemical problems.[1,2] Since N^6,N^6-dimethyladenosine has been found to be a minor base occurring in the RNA of several bacteria,[3] it was of interest to determine the position of alkylation. Such evidence would be useful in the identification of fragments derivable from alkylated RNA which contains N^6,N^6-dimethyladenine as one of its constituent bases.

Methylation of N^6,N^6-dimethyladenine with dimethyl sulfate produced the 1-, 3-, and 9-methyl derivatives[4,5]; no studies have been described of alkylation of N^6,N^6-dialkyl-3-, -7-, or -9-substituted adenines. We chose N^6,N^6-diethyl-9-methyladenine (1), available from another investigation, for methylation study.

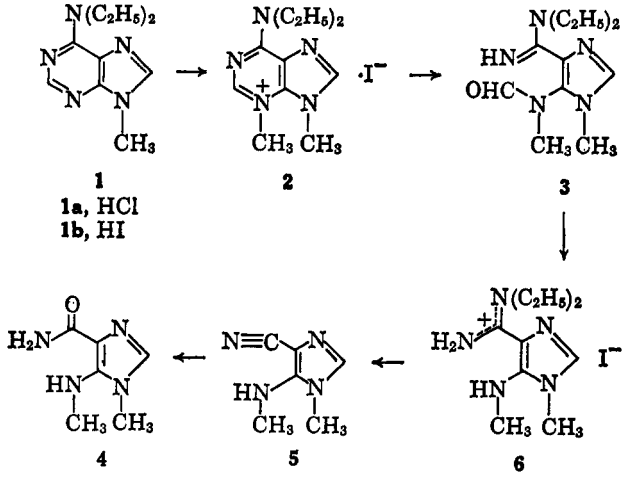
N^6,N^6-Diethyl-9-methyladenine (1)[6] was synthesized in the classical manner from 4,6-dichloro-5-nitropyrimidine.[7] Monosubstitution was readily accomplished by reaction with 2 equiv. of diethylamine in ether at −40° to give 4-chloro-6-diethylamino-5-nitropyrimidine. Reaction of the latter with aqueous methylamine at room temperature for 2 hr. gave 73% (from dichloronitropyrimidine) of pure 6-diethylamino-4-methylamino-5-nitropyrimidine as a viscous oil, which was further characterized as its crystalline picrate. Reduction of the diaminonitropyrimidine with hydrogen and Raney nickel gave 79% of 5-amino-4-diethylamino-6-methylaminopyrimidine. Cyclization in refluxing ethyl orthoformate–acetic anhydride[8,9] afforded the hydrochloride **1a** of the desired purine in 69% yield.

Reaction of N^6,N^6-diethyl-9-methyladenine (1) with methyl iodide in boiling ethanol for 24 hr. gave, in addition to 17% of recovered 1, 41% of a crystalline water-soluble methiodide. Based on ultraviolet spectral properties (see Experimental Section) and alkaline degradation, the structure of this quaternary iodide was unequivocally shown to be 6-diethylamino-3,9-dimethylpurinium iodide (2). Thus the site of alkylation of 1 is N-3 and this same alkylation site is expected with N^6,N^6-dimethyladenosine and 2′-deoxy-N^6,N^6-dimethyladenosine. This is in contradistinction to

(1) *Cf.* G. Schmidt, *Ann. Rev. Biochem.*, **33**, 674 (1964).
(2) J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **85**, 193 (1963).
(3) J. W. Littlefield and D. B. Dunn, *Biochem. J.*, **70**, 642 (1958).
(4) L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard [*J. Am. Chem. Soc.*, **86**, 5320 (1964)] have shown that the 6-dimethylamino-"7"-substituted purines of B. R. Baker, R. E. Schaub, and J. P. Joseph [*J. Org. Chem.*, **19**, 638 (1954)] are, in reality, 6-dimethylamino-3-substituted purines.
(5) B. C. Pal and C. A. Horton, *J. Chem. Soc.*, 400 (1964).
(6) Previously prepared by R. K. Robins and H. H. Lin [*J. Am. Chem. Soc.*, **79**, 490 (1957)] by displacement of chloride from 6-chloro-9-methylpurine with diethylamine.
(7) W. R. Boon, W. G. M. Jones, and G. R. Ramage, *J. Chem. Soc.*, 96 (1951).
(8) L. Goldman, J. W. Marsico, and A. L. Gazzola, *J. Org. Chem.*, **21**, 599 (1956).
(9) J. A. Montgomery, *J. Am. Chem. Soc.*, **78**, 1928 (1956).

adenosine and 2′-deoxyadenosine which methylate at N-1.[2]

Methylation of purine **1** resulted in a large bathochromic shift in the ultraviolet maxima of quaternary purine **2** ($\lambda_{max}^{0.1\ N\ HCl}$ 288 mμ) compared with that of **1** ($\lambda_{max}^{0.1\ N\ HCl}$ 271 mμ). This effect was first observed by Clark, Todd and Zussman[10] on intramolecular alkylation at N-3 in the conversion of 2′,3′-O-isopropylidene-5′-O-*p*-toluenesulfonyladenosine to the quaternary 3,5′-cyclonucleoside salt, 3,5′-cyclo-2′,3′-O-isopropylideneadenosine *p*-toluenesulfonate. In further support of the structural assignment **2**, it may be noted that 3-methyladenine exhibits λ_{max}^{acid} 274 mμ,[11] a bathochromic shift of 14 mμ from adenine (λ_{max}^{acid} 260 mμ),[12] whereas 1-methyladenine exhibits λ_{max}^{acid} 259 mμ,[13] essentially no shift from adenine. The large bathochromic shift effected by N-3 alkylation is also demonstrated by pyrotriacanthine chloride (λ_{max}^{EtOH} 275 mμ)[14] compared with that of adenosine (λ_{max}^{acid} 260 mμ).[12] The low ε value for the ultraviolet maximum at 287.5 mμ exhibited in 0.1 *N* sodium hydroxide by the quaternary purine **2** was indicative of degradation, previously noted for cyclonucleosides[10,15] and for pyrotriacanthine.[14]



1
1a, HCl
1b, HI
2
3
4
5
6

When quaternary purine **2** was allowed to stand in 0.1 *N* sodium hydroxide for 22.5 hr. at room temperature, the absorption maximum in base at 287.5 mμ disappeared with the production of a broad, low-intensity plateau centered at about 290 mμ.[16] The resulting product was obtained as a hydriodide salt which exhibited infrared absorption bands indicating an imidazoleformamidinium salt.[17] This product (67% yield) was assigned structure **6**, N,N-diethyl-1-methyl-5-methylamino-4-imidazolecarboxamidine hydriodide, and would be expected to result from hydroxide attack on **2** at C-2 with opening of the pyrimidine ring and initial formation of the 5-formamido-4-imidazolecarboxamidine **3**,[18] followed by hydrolytic removal of the formyl group.

The 4-imidazolecarboxamidine **6** was degraded further by treatment with 1 *N* sodium hydroxide for 2 hr. at 100°, thereby producing an aminoimidazolecarbonitrile (λ_{max}^{KBr} 4.55 μ) in 3% yield; the formula, $C_6H_8N_4$, was indicated by elemental analyses. In acid, maxima were observed at 240 and 260 mμ[19] and in base at 250 mμ. These data are consistent with the assignment of structure **5**, 1-methyl-5-methylamino-4-imidazolecarbonitrile.

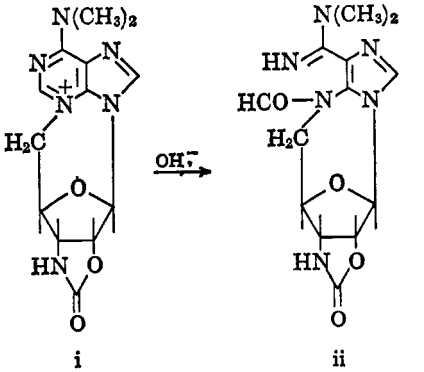
The main product of the reaction (54% yield), $C_6H_{10}N_4O$, exhibited infrared bands indicative of an imidazolecarboxamide (5.99 and 6.24 μ) bearing an amine substituent (3.00 and 3.15 μ) and was assigned structure **4**, 1-methyl-5-methylamino-4-imidazolecarboxamide. Results of the Bratton and Marshall test[20] with this product were negative, thus showing that the 5-amino group of **4** (originally N-3 of **2**) was substituted. The nitrile **5** would result by removal of the protons from the amidinium ion of **6** followed by elimination of diethylamine. Hydrolysis of nitrile **5** then produced carboxamide **4**.

The well-resolved proton magnetic resonance (p.m.r.) spectrum[21] of **4** was in full agreement with the structural assignment. The N-1–CH_3 was observed as a sharp singlet at δ 3.64 and was used as an internal standard for integration. The following additional assignments were made: sharp one-proton singlet at δ 7.37, C-2–H[22]; broad two-proton multiplet centered at 6.98, $CONH_2$; one-proton multiplet at 5.88, C-5–NH; and three-proton doublet centered at 2.92, C-5–NCH_3.

Confirmation of the structural designation **4** for the alkaline degradation product of quaternary purine **2** was obtained by synthesis of **4**.

Lithium aluminum hydride reduction of 5-formamido-1-methyl-4-imidazolecarboxamide (**8**), obtained in 62% yield by the action of acetic anhydride–formic acid[23]

(18) A similar 5-formamidoimidazole-4-carboxamidine (ii) was isolated by Baker and Joseph[15] on alkaline degradation of i.



i ii

(19) The related 4-amino-1-methyl-5-imidazolecarbonitrile hydrochloride exhibits maxima at 233 and 266 mμ: R. N. Prasad and R. K. Robins, *J. Am. Chem. Soc.*, **79**, 6401 (1957).

(20) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537 (1939).

(21) The p.m.r. spectrum was determined with a Varian Model A-60 spectrometer using deuterated dimethyl sulfoxide as a solvent. Chemical shifts (δ) are given in parts per million from tetramethylsilane.

(22) Similar protons are observed at δ 7.71 and 7.60 for imidazole and caffeine, respectively: "Varian High Resolution NMR Spectra Catalog," Varian Associates, Instrument Division, Palo Alto, Calif., 1962, spectra 20 and 204.

(23) E. Shaw, *J. Biol. Chem.*, **185**, 439 (1950).

(10) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

(11) G. B. Elion, *J. Org. Chem.*, **27**, 2478 (1962).

(12) J. M. Gulland and E. R. Holiday, *J. Chem. Soc.*, 765 (1936).

(13) P. Brookes and P. D. Lawley, *ibid.*, 539 (1960).

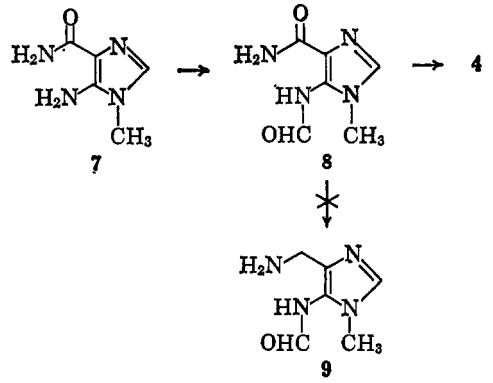
(14) N. J. Leonard and J. A. Deyrup, *J. Am. Chem. Soc.*, **84**, 2148 (1962).

(15) B. R. Baker and J. P. Joseph, *ibid.*, **77**, 15 (1955).

(16) For the effect of steric inhibition of resonance on ultraviolet spectra, *cf.* H. H. Jaffé and M. Orchin, "Theory and Application of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p. 411.

(17) J. C. Grivas and A. Taurins, *Can. J. Chem.*, **37**, 1260 (1959).

on 5-amino-1-methyl-4-imidazolecarboxamide (7),[24] gave a product in low yield which was identical with the alkaline degradation product, $C_6H_{10}N_4O$. The major reduction product was 9-methylhypoxanthine.[6,25] Two possible monoamides which could result from reduction of **8** are **4** and **9**, but the latter is excluded since such a structure cannot be derived by alkaline degradation of any possible quaternary methylation product of **1**.



Experimental Section

Melting Points.—Melting points were taken on a Kofler hot stage and are corrected except those specified "(cap.)" which were taken in soft glass capillaries and are uncorrected.

Absorption Spectra.—Ultraviolet absorption spectra were determined by means of a Cary recording spectrophotometer and infrared spectra were measured in potassium bromide disks by means of a Perkin-Elmer spectrophotometer (Model 21).

4-Chloro-6-diethylamino-5-nitropyrimidine.—To a magnetically stirred solution of 5.82 g. (0.030 mole) of 4,6-dichloro-5-nitropyrimidine[7] in 150 ml. of anhydrous ether, chilled to −40° by means of a Dry Ice bath, was added dropwise over 1 hr. a solution of 6.15 ml. (4.38 g., 0.060 mole) of diethylamine in 50 ml. of anhydrous ether. The stirred mixture was gradually allowed to warm to 15° during 1 hr. and the precipitated diethylamine hydrochloride was removed by filtration and washed with ether. The combined filtrate and wash were evaporated *in vacuo* to a tan oil which was sublimed at 40–50° (0.1 mm.) to give 5.90 g. of yellow crystals. Recrystallization from heptane with the aid of Norit gave 5.39 g. (78%) of product as yellow crystals: m.p. 33–34°; $\lambda_{max}^{0.1\ N\ HCl}$ 254 mμ (ε 14,800); λ_{max}^{MeOH} 253 mμ (ε 14,600); $\lambda_{max}^{0.1\ N\ NaOH}$ 251 mμ (ε 11,800).

Anal. Calcd. for $C_8H_{11}ClN_4O_2$: C, 41.6; H, 4.81; Cl, 15.4; N, 24.3. Found: C, 41.6; H, 5.25; Cl, 15.8; N, 24.1.

6-Diethylamino-4-methylamino-5-nitropyrimidine.—To a dioxane solution of crude 4-chloro-6-diethylamino-5-nitropyrimidine from 1.94 g. (0.01 mole) of 4,6-dichloro-5-nitropyrimidine was added 5.0 ml. of 25% methylamine. The reaction mixture became hot and after 2 hr. was evaporated *in vacuo* to a mixture of crystals and gum. The mixture was partitioned between water and ether and the ether solution was washed with 5% sodium bicarbonate and water. The combined aqueous washes were re-extracted with ether and the combined ether extracts were evaporated *in vacuo* to give 1.66 g. (73% from 4,6-dichloro-5-nitropyrimidine) of product as a tan viscous oil.

Anal. Calcd. for $C_9H_{15}N_5O_2$: C, 48.0; H, 6.71; N, 31.1. Found: C, 48.0; H, 6.85; N, 31.0.

A picrate was prepared in aqueous acetic acid and recrystallized twice from absolute ethanol to give yellow crystals, m.p. 165.5–166.5°.

Anal. Calcd. for $C_9H_{15}N_5O_2 \cdot C_6H_3N_3O_7$: C, 39.6; H, 3.99; N, 24.7. Found: C, 39.8; H, 3.95; N, 25.0, 24.6.

5-Amino-4-diethylamino-6-methylaminopyrimidine.—A solution of 1.58 g. (0.00711 mole) of 6-diethylamino-4-methylamino-5-nitropyrimidine in 80 ml. of 2-methoxyethanol containing one teaspoon of Raney nickel catalyst was hydrogenated at atmospheric pressure until absorption of hydrogen ceased (40 min.). The filtered catalyst was washed with 2-methoxyethanol and the combined filtrate and washings were evaporated *in vacuo* to give 1.23 g. of light tan crystalline residue, m.p. 110–114°. Recrystallization from heptane gave 1.10 g. (79%) of product as tan crystals, m.p. 117–120°. Three additional recrystallizations from cyclohexane gave pale pink crystals: m.p. 120.5–122°; $\lambda_{max}^{0.1\ N\ HCl}$ 236, 240 (infl.), and 310 mμ (ε 9400, 9280, and 12,200); λ_{max}^{EtOH} 295 mμ (ε 11,700); $\lambda_{max}^{0.1\ N\ NaOH}$ 231 and 292 mμ (ε 11,900 and 10,400).

Anal. Calcd. for $C_9H_{17}N_5$: C, 55.4; H, 8.78; N, 35.9. Found: C, 55.7; H, 8.61; N, 35.7.

N^6,N^6-Diethyl-9-methyladenine (1).—A solution of 77.5 g. (0.396 mole) of 5-amino-4-diethylamino-6-methylaminopyrimidine in 300 ml. of ethyl orthoformate and 300 ml. of acetic anhydride was boiled under reflux for 4 hr. and evaporated to dryness *in vacuo*. A solution of the residual oil in 700 ml. of methanolic hydrogen chloride was evaporated *in vacuo* to give a dark semicrystalline residue to which acetone and methanol were added. The resulting tan crystals were collected by filtration and air dried to yield 54.6 g. of crude hydrochloride **1a**, m.p. 172–178°, sintering at 138–143°. Concentration of the filtrate gave an additional 12.9 g., m.p. 168–174°, sintering at 138–145°, giving a total yield of 67.5 g. (69%). Recrystallization of the combined crops from chloroform–ether gave 51.2 g. of **1a** as tan crystals: m.p. 176–179°, sintering at 150–155°; $\lambda_{max}^{0.1\ N\ HCl}$ 271 mμ (ε 16,800); λ_{max}^{MeOH} 275 mμ (ε 16,300); $\lambda_{max}^{0.1\ N\ NaOH}$ 278 mμ (ε 17,700).

Anal. Calcd. for $C_{10}H_{15}N_5 \cdot HCl \cdot 0.25H_2O$: C, 48.4; H, 6.76; Cl, 14.4; N, 28.4. Found: C, 48.7; H, 7.00; Cl, 14.7; N, 28.2.

A solution of 32.7 g. (0.133 mole) of hydrochloride **1a** in 450 ml. of water was made basic with sodium carbonate and extracted with three 200-ml. portions of chloroform. The combined extracts were dried over magnesium sulfate and filtered, and the filtrate evaporated *in vacuo* to give 26.0 g. (99%) of **1** as a brown oil, lit.[6] m.p. 48–50°.

6-Diethylamino-3,9-dimethylpurinium Iodide (2).—A solution of 27.0 g. (0.132 mole) of **1** and 60 ml. of methyl iodide in 300 ml. of absolute ethanol was heated under reflux for 24 hr. and then chilled and filtered to yield 41.2 g. of colorless crystals, m.p. 177–218° dec. Recrystallization from absolute ethanol gave 7.40 g. (17%) of colorless crystals of recovered crude **1** as the hydriodide **1b**, m.p. 200–208° dec.

Anal. Calcd. for $C_{10}H_{15}N_5 \cdot HI$: C, 36.0; H, 4.84; I, 38.1; N, 21.0. Found: C, 35.9; H, 4.97; I, 37.4; N, 20.5.

The ethanol filtrate was evaporated to dryness *in vacuo* to give a crystalline residue which was recrystallized from 1 l. of acetone containing a small amount of water to afford, in three crops, 17.6 g. of crude **2** as colorless crystals, m.p. 218–232° dec. Recrystallization from absolute ethanol gave 15.8 g. (34%) of colorless crystals, m.p. 229–232° dec. A sample, recrystallized from absolute ethanol, gave pale yellow needles: m.p. 231.5–232.5° dec.; $\lambda_{max}^{0.1\ N\ HCl}$ 288 mμ (ε 18,300); λ_{max}^{MeOH} 289 mμ (ε 18,400); $\lambda_{max}^{0.1\ N\ NaOH}$ 287.5 mμ (broad) (ε 3470); λ_{max}^{KBr} 6.14 and 6.26 μ.

Anal. Calcd. for $C_{11}H_{18}IN_5$: C, 38.0; H, 5.22; I, 36.6; N, 20.2. Found: C, 37.9; H, 5.15; I, 36.4; N, 19.8.

Alkaline Degradation of 6-Diethylamino-3,9-dimethylpurinium Iodide (2).—A solution of 0.500 g. (0.00144 mole) of **2** in 20 ml. of 0.1 *N* sodium hydroxide was allowed to stand at room temperature for 22.5 hr., after which solid carbon dioxide was added to lower the pH to 8.5. The resulting solution was evaporated to dryness *in vacuo* and the residue was slurried with 15 ml. of hot absolute ethanol and filtered. The filtrate was evaporated to dryness *in vacuo*, the residue was triturated with 7 ml. of absolute ethanol and filtered, and the filtrate was evaporated *in vacuo* to a small volume and diluted with ether. Filtration gave 0.390 g. of colorless precipitate which was triturated with 40 ml. of acetone and filtered. Evaporation of the filtrate yielded 0.354 g. (71%) of 1-methyl-5-methylamino-4-(N,N-diethyl)imidazolecarboxamidine hydriodide (**6**) as colorless crystals, m.p. 117–124° (cap.). The compound was adsorbed on Norit from an ethyl acetate solution and eluted with five 50-ml. portions of hot methanol. Evaporation *in vacuo* of the combined eluates gave a crystalline residue which was recrystallized from ethyl acetate–ethanol to give 0.082 g. (17%) of colorless crystals, m.p. 102–105.5° (cap.). Drying *in vacuo* over phosphoric anhydride at 64° for 3 hr. gave $6 \cdot 0.4H_2O$ as colorless crystals: m.p. 138–

(24) A. H. Cook, J. D. Downer, and I. Heilbron, *J. Chem. Soc.*, 2028 (1948).

(25) 5-Formamido-4-imidazolecarboxamide yields hypoxanthine when refluxed with aqueous potassium bicarbonate or with sodium ethoxide in ethanol (ref. 23).

139° (cap.); $\lambda_{max}^{0.1\ N\ HCl}$ 288 mμ (ε 5010); $\lambda_{max}^{H_2O}$ 295 mμ (ε 4500); $\lambda_{plateau}^{0.1\ N\ NaOH}$ 290 mμ (ε 1870); λ_{max}^{KBr} 2.86, 3.05, and 3.23 (⩾$\overset{+}{N}H$, =$\overset{+}{N}H_2$, and NH), 5.85 and 5.95 (C=$\overset{+}{N}$ and =$\overset{+}{N}H_2$), and 6.16 and 6.20 μ (C=C and C=N).

Anal. Calcd. for $C_{10}H_{20}IN_5 \cdot 0.4H_2O$: C, 34.9; H, 6.09; I, 36.8; N, 20.3. Found: C, 35.2; H, 6.21; I, 36.7; N, 19.9.

A solution of 4.00 g. (0.0115 mole) of **2** in 120 ml. of 1 *N* sodium hydroxide was heated on a steam bath for 2 hr. and allowed to stand at room temperature overnight. The solution was extracted with six 120-ml. portions of chloroform and the combined extracts were evaporated to dryness. The tan crystalline residue was recrystallized from ethanol–ethyl acetate with the aid of Norit to give 0.950 g. (54%) of 1-methyl-5-methylamino-4-imidazolecarboxamide (**4**) as colorless crystals: m.p. 211–213°; $\lambda_{max}^{0.1\ N\ HCl}$ 252 and 268 mμ (ε 6970 and 6480); λ_{max}^{MeOH} 269 mμ (ε 9220); $\lambda_{max}^{0.1\ N\ NaOH}$ 267.5 mμ (ε 8890); λ_{max}^{KBr} 3.00 and 3.05 (NH and NH_2), and 5.99 and 6.24 μ ($CONH_2$ and C=N).

Anal. Calcd. for $C_6H_{10}N_4O$: C, 46.7; H, 6.54; N, 36.3. Found: C, 46.8; H, 6.38; N, 36.0.

Results of the Bratton–Marshall[20] test with compound **4** were negative for primary aromatic amine, but positive with 4-amino-5-imidazolecarboxamide hydrochloride.

Evaporation *in vacuo* of the mother liquor from **4** and recrystallization of the residue from water gave 0.043 g. (3%) of 1-methyl-5-methylamino-4-imidazolecarbonitrile **5** as colorless crystals: m.p. 244–245°; $\lambda_{max}^{0.1\ N\ HCl}$ 240 and 260 mμ (ε 8040 and 6200); λ_{max}^{EtOH} 250 mμ (ε 10,300); $\lambda_{max}^{0.1\ N\ NaOH}$ 250 mμ (ε 9400); λ_{max}^{KBr} 3.05, 3.20, and 3.38 (NH), 4.55 (C≡N), and 6.10 and 6.23 μ (C=C and C=N).

Anal. Calcd. for $C_6H_8N_4$: C, 52.9; H, 5.92; N, 41.2. Found: C, 53.3; H, 5.85; N, 41.7, 41.3.

5-Formamido-1-methyl-4-imidazolecarboxamide (8).—To a suspension of 2.80 g. (0.020 mole) of 5-amino-1-methyl-4-imidazolecarboxamide (**7**)[24] in 10 ml. of 97% formic acid was added 20 ml. of acetic anhydride. After the initial vigorous bubbling had subsided, the solution was heated at 70° for 30 min. and then evaporated *in vacuo* to a pink crystalline residue. Ten milliliters of ice-cold water was added to the residue and the crystals were collected by filtration, triturated with ice-cold saturated sodium bicarbonate solution, and air dried to yield 3.25 g. of pink crystals of crude **8**, m.p. 174–177° (gas evolution), resolidifying and slowly decomposing above 225°. Recrystallization from aqueous ethanol with the aid of Norit gave 2.10 g. (62%) of **8** as colorless crystals, m.p. 247–252° (**8** resolidified and did not melt up to 300°); $\lambda_{max}^{0.1\ N\ HCl}$ 217 mμ (ε 11,400); λ_{max}^{MeOH} 245 mμ (broad infl.) (ε 8240); $\lambda_{max}^{0.1\ N\ NaOH}$ 265 mμ (ε 8740); λ_{max}^{KBr} 3.00 and 3.17 (NH and NH_2), 5.84 (NHCHO), and 6.00 and 6.26 μ ($CONH_2$ and C=N).

Anal. Calcd. for $C_6H_8N_4O_2$: C, 42.8; H, 4.80; N, 33.3. Found: C, 42.9; H, 4.58; N, 33.6.

Lithium Aluminum Hydride Reduction of 5-Formamido-1-methyl-4-imidazolecarboxamide (8). A. In Refluxing Ether–Dioxane.—To a stirred suspension of 1.10 g. (0.029 mole) of lithium aluminum hydride in 30 ml. of ether and 40 ml. of dioxane was added 1.00 g. (0.00595 mole) of **8** in small portions. The mixture was stirred and heated under reflux for 2 days, cooled to room temperature, and diluted with 50 ml. of ether. Excess hydride was decomposed by careful dropwise addition of 5 ml. of ethanol, 5 ml. of water, and 20 ml. of 2.5 *N* sodium hydroxide. The organic solvent was decanted from the residual sludge which was extracted by trituration with two 50-ml. portions of ether. The combined organic extracts were dried over magnesium sulfate and filtered, and the filtrate was evaporated *in vacuo* to give 0.035 g. of colorless crystals. Thin layer chromatography on cellulose (preparative scale) in the system, isopropyl alcohol–ammonia–water (7:1:2), showed the presence of four ultraviolet-absorbing components having R_f 0.52, 0.64, 0.77, and 0.89. In this system, 1-methyl-5-methylamino-4-imidazolecarboxamide (**4**), obtained by alkaline degradation of **2**, had R_f 0.81 and 9-methylhypoxanthine[6] had R_f 0.55. The band with R_f 0.77, corresponding to **4**, was removed from the plate and extracted by heating with 20 ml. of absolute ethanol. Evaporation of the solvent gave 0.016 g. of crude **4** as tan crystals.

The basic sludge insoluble in the organic layer was taken up in 10 ml. of water and diluted with absolute ethanol. The colorless crude sodium salt thus obtained was removed by filtration, washed with absolute ethanol and ether, and dissolved in 10 ml. of water. When neutralized with glacial acetic acid, the resulting colorless crystals of 9-methylhypoxanthine were collected by filtration and washed with absolute ethanol to yield 0.188 g. (21%). Recrystallization from 8 ml. of boiling water afforded 0.167 g. of colorless crystals (unmelted up to 300°): $\lambda_{max}^{0.1\ N\ HCl}$ 251 mμ (ε 9150); λ_{max}^{MeOH} 248 mμ (ε 9220); $\lambda_{max}^{0.1\ N\ NaOH}$ 254 mμ (ε 10,300) [lit.[6] $\lambda_{max}^{pH\ 1}$ 251 mμ (ε 6300); $\lambda_{max}^{pH\ 11}$ 256 mμ (ε 7350)].

Anal. Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.03; N, 37.3. Found: C, 48.0; H, 4.19; N, 37.7.

B. Soxhlet Procedure in Refluxing Dioxane.—A stirred suspension of 1.10 g. (0.029 mole) of lithium aluminum hydride in 150 ml. of dioxane was heated under reflux for 7 days in a Soxhlet apparatus containing 0.956 g. (0.00578 mole) of powdered **8** in the thimble. Excess hydride was destroyed as in A above. The combined dioxane decantate and ether extracts were dried over magnesium sulfate and filtered, and the filtrate was evaporated *in vacuo* to give 0.643 g. of a brown oil which partially crystallized on standing overnight. A solution of the crude material in 35 ml. of chloroform was chromatographed on a 30-g. column of silica gel. Elution with ethyl acetate–methanol (4:1) and evaporation of the eluate gave a gum. Crystallization from ethanol–ethyl acetate gave 0.018 g. of **4** as tan crystals. The samples of **4** from A and B were combined and sublimed at 125° (0.07 mm.) to give 0.031 g. of colorless crystals. Two recrystallizations from absolute ethanol afforded 0.016 g. of colorless crystals of **4**, m.p. 211–213° dec., undepressed on admixture with material obtained by hot alkaline degradation of **2**. The two preparations exhibited identical infrared and ultraviolet spectra and X-ray diffraction powder diagrams.

Acknowledgment.—We wish to thank Mr. L. M. Brancone and staff for microanalyses, Mr. W. Fulmor and staff for spectral determinations, and Mr. G. P. Chrekian for the X-ray diffraction powder measurements.