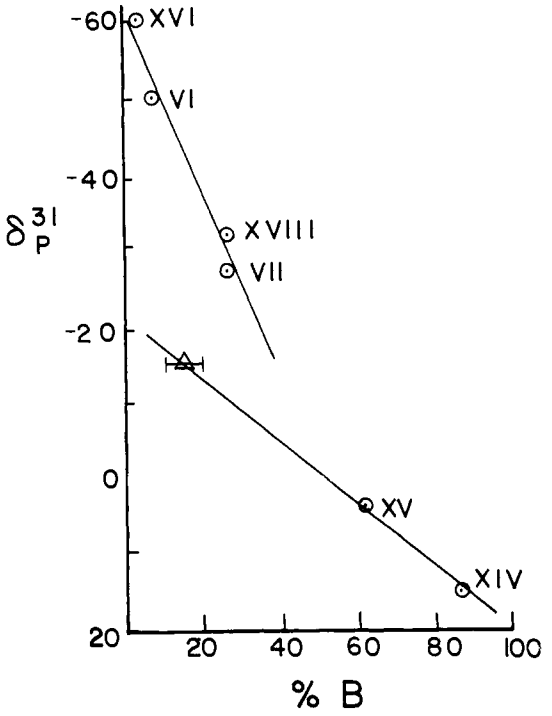

Figure 6. Plot of ^{31}P chemical shift vs. percent along the Berry coordinate for PO_2C_3 compounds. Point labels are from Table II. The triangle plotted point is for an estimated structure. (See text.)

has $\delta_{^{31}P} = -1.5$.[2] On the basis of structural data on similar compounds (e.g., see Table III), one would expect this molecule to have a % B value of 10–20. If the reported $\delta_{^{31}P}$ value is plotted at % B = 15 on Figure 6, we see that this point falls on a straight line containing the points for compounds XIV and XV, and this line is different form the line through the remaining four points. Thus, it appears that for PO_2C_3 species there are two distinct correlation lines in Figure 6. The compounds of these two correlations can be distinguished on the basis of the relative orientations of their P–O bonds. The relative orientations can be discussed in terms of the orientations that the P–O bonds would have if a Berry rotation converted the species to a pure SP configuration or a TBP configuration. The species represented on the upper line of Figure 6 would have two axial P–O bonds in the TBP configuration. Those represented on the lower line would have axial/equatorial orientations in the TBP arrangement or two adjacent basal P–O bonds in the SP. A definite structure vs. chemical shift relationship is apparent in this figure, but whether it is due to changes in geometry or changes in the electronic substituent effects of individual substituents is not clear. There is, in any case, a large change in chemical shift for chemically similar compounds. This variation shows again that one must take care in using phosphorus chemical shifts to determine molecular structures.

The principal purpose in presenting the data in Table III has been to stimulate and lay groundwork for further studies. As can be seen in Figures 4, 5, and 6, not enough points are on the plots to establish unequivocally any explicit relationships between chemical shift and molecular structure. With more data on well-characterized compounds these relationships could be tested more definitively. Such relationships could be important in providing a sound basis for the use of NMR parameters to characterize molecular structure. A more fundamental use of the relationships would be their interpretation in terms of the nature of bonding in these types of molecules. In any case, the present work has demonstrated the ability of NMR to provide a bridge between the crystalline states and liquid (e.g., solution) states. In the present application it has been shown that the structures of representative phosphoranes are very similar in solution to the X-ray-characterized solid-state structures.

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Registry No. I, 19613-06-0; II, 32394-39-1; III, 3009-75-4; IVa, 19579-02-3; IVb, 21229-04-9; IVc, 6857-81-4; IVd, 21229-05-0; V, 60011-07-6; XV, 79734-98-8; XVII, 2588-88-7; XVIII, 79768-48-2; XIX, 79734-99-9; XXVII, 38575-00-7; XXIX, 61733-80-0; XXXI, 58498-98-9; XXXV, 54554-57-3; $BrP(C_6H_5)_4$, 24038-30-0.

5-Methyladenine: A Transient Intermediate in a Translocative Rearrangement

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Contribution from the Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801. *Received June 22, 1981*

Abstract: A synthetic approach to 5-methyl-5*H*-adenine by closure of a pyrimidine ring onto 5-amino-4-cyano-4-methyl-4*H*-imidazole, by mild treatment with formamidine at 20 °C, resulted in rearrangement to 4-amino-8-methylimidazo[1,5-*a*]-1,3,5-triazine. This constitutes a "translocative rearrangement" in which the overall result is to remove a C≡N group from the quaternary carbon of the original 4*H*-imidazole ring and to translocate it efficiently and with ease to a ring nitrogen two atoms removed, where it becomes attached as a $\gtrdot CNH_2$ function. An intramolecular route is postulated, proceeding through 5-methyl-5*H*-adenine (and/or its tautomers) as a transient intermediate. Application of semiempirical molecular orbital MINDO/3 calculations revealed the relative instability of the intermediate 5-methyladenine and the stability of the final rearrangement product. They also provided insight into the probable loci of bond breaking and into the structures of the potential intermediates in the ring opening of 5-methyladenine. The imidazotriazine structure of the rearrangement product, indicated by spectroscopic data, was established by unequivocal synthesis.

Previous experimental results in this laboratory have indicated that the existence of a C5-alkylated guanine would be transient and that an intermediate of this type, if formed, would tend to undergo facile ring cleavage and/or rearrangement.[1-3] While it is altogether possible that a C5-alkylated adenine would also be destabilized, the electron-donating 6-amino group might offer greater hope for the recognition of such a species. The least

(1) Golankiewicz, B.; Holtwick, J. B.; Holmes, B. N.; Duesler, E. N.; Leonard, N. J. *J. Org. Chem.* **1979**, *44*, 1740.

(2) Holtwick, J. B.; Golankiewicz, B.; Holmes, B. N.; Leonard, N. J. *J. Org. Chem.* **1979**, *44*, 3835.

(3) Holtwick, J. B.; Leonard, N. J. *J. Org. Chem.* **1981**, *46*, 3681.

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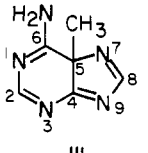
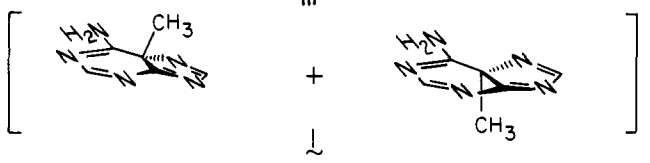
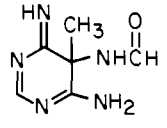
sterically hindered member of the series, 5-methyladenine or, more descriptively, 5-methyl-5*H*-adenine (**1**, racemate), bears an intriguing structural relationship to adenine. Scale molecular models suggest that the tetrasubstituted carbon at position 5 causes a slight puckering of the nonaromatic ring system. Thus, viewed from the face away from the methyl group, the topography of 5-methyladenine is remarkably similar to that of adenine itself. Viewed from the other side, the methyl group protrudes orthogonally from the ring system. The 1,N^6-hydrogen bonding capability of adenine is preserved; the stacking of ring upon ring would be blocked; and substitution at N9 would place a positive charge on the ring system. Syntheses aimed at 5-methyladenine (**1**) as an unusual target could well lead to new rearrangements involving **1** as a transient intermediate.



1





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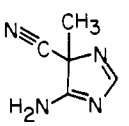
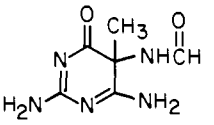


3



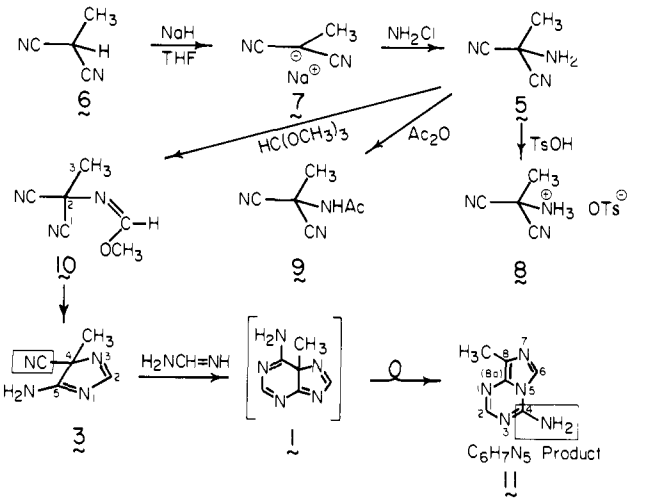
4

Synthesis

Two general synthetic sequences leading toward **1** appeared possible: (a) fusion of an imidazole moiety onto an appropriately substituted dihydropyrimidine (**2**) and (b) construction of a pyrimidine ring onto a suitably substituted 4*H*-imidazole (**3**). The two key precursors that could serve both routes were 2-amino-2-cyanopropionitrile and formamidine. The substituted dihydropyrimidine-type intermediate **2**, which is analogous to the 2,6-diamino-4,5-dihydro-5-formamido-5-methylpyrimidin-4-one (**4**) that preceded the formation and rearrangement of 5-methylguanine,[2] could theoretically result from a condensation of the two cyano groups of N-protected 2-amino-2-cyanopropionitrile with free formamidine as in the method of Baddiley, Lythgoe, and Todd.[4] The substituted 4*H*-imidazole could result from ring closure involving the amino function and one of the cyano groups of 2-amino-2-cyanopropionitrile (**5**) with formamidine acetate, as in the method of Ferris and Orgel.[5]

Of the possible approaches to 2-amino-2-cyanopropionitrile (**5**), (a) cyanation of aminopropionitrile, (b) methylation of aminomalononitrile, and (c) amination of methylmalononitrile, the last offered the greatest chance for success. Among the available aminating agents, *O*-mesitylenesulfonylhydroxylamine[6-8] and hydroxylamine *O*-sulfonic acid[9] have been employed mainly for N-amination, whereas chloramine has been shown to react with malonate carbanions to give C-aminated products in high yields.[10] We therefore chose chloramine. Methylmalononitrile (**6**)[11] was

Scheme I



obtained from methylmalonamide[12] and phosphorus pentoxide by vacuum distillation. The preparation of methylmalonamide from diethyl methylmalonate by heating with anhydrous ammonia at 110 °C in a steel bomb greatly improved the yield of the diamide (98–100%) compared with that obtained by refluxing the diester with ammonium hydroxide (40–50%).[13] The sodio derivative (**7**) of methylmalononitrile, prepared by treatment of **6** with sodium hydride in tetrahydrofuran, was allowed to react with an ethereal solution of monochloramine[14] to obtain the required 2-amino-2-cyanopropionitrile (**5**) as a colorless oil (62% yield) (Scheme I). Since the compound was unstable and turned dark on exposure to air for a few hours, it was used directly in the next stage of the synthesis. A stable, crystalline tosylate salt (**8**) was prepared by treatment with an ethereal suspension of *p*-toluenesulfonic acid. A crystalline *N*-acetyl derivative (**9**), which could be a useful precursor to an intermediate of type **2**, was prepared by heating with acetic anhydride.

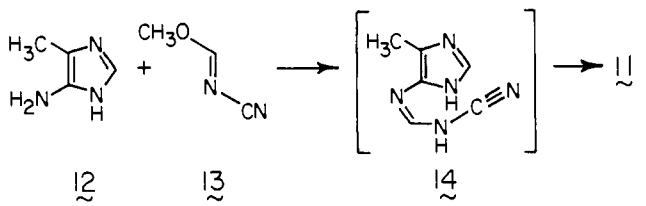
The ^{13}C NMR spectrum of every member of the designed synthetic sequence, starting with compound **5**, became crucial in this study since a check for the presence of a quaternary carbon in the final product provided a facile means of distinguishing between structure **1** and any other structure arising from possible rearrangement(s),[1,2] at any stage of the synthesis,[15] in a simple drive for aromaticity. The ^{13}C NMR of 2-amino-2-cyanopropionitrile (**5**) in deuterated dimethyl sulfoxide (with tetramethylsilane as an internal reference standard) revealed three signals: the quaternary carbon at δ 43, the methyl resonance at 26 and the two nitriles at 118 ppm.

For the incipient closure of the 5-membered ring, 2-amino-2-cyanopropionitrile (**5**) was treated with trimethyl orthoformate, with formic acid as a catalyst, to give 2-cyano-2-(methoxymethyleneamino)propionitrile (**10**) which, unlike its precursor, was stable and could be stored in a desiccator for several days. When crude **5** was treated directly with trimethyl orthoformate in an attempt to minimize loss of material resulting from the instability of **5** or from decomposition during distillation, the yield of **10** could be increased. However, the product was then accompanied by a small amount of side product, 2-cyano-2-(methoxymethyleneamino)propionamide, which was separable by filtration. The ^{13}C NMR spectrum of compound **10** revealed the maintenance of the crucial quaternary carbon by resonance at δ 49. The ring closure of **10** to 5-amino-4-cyano-4-methyl-4*H*-imidazole (**3**) was accomplished in 2-propanol saturated with ammonia at 0 °C.

The substituted 4*H*-imidazole **3** exhibited several interesting physical and chemical properties that are worth noting. The ^1H

(4) Baddiley, J.; Lythgoe, B.; Todd, A. R. *J. Chem. Soc.* **1943**, 387.
(5) Ferris, J. P.; Orgel, L. E. *J. Am. Chem. Soc.* **1966**, *88*, 3829.
(6) Tamara, Y.; M amikawa, J.; Miki, Y.; Matsugashita, S. *Tetrahedron Lett.* **1972**, 4133.
(7) Tamara, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.
(8) Wiemer, D. F.; Leonard, N. J. *J. Org. Chem.* **1974**, *39*, 3438.
(9) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; John Wiley and Sons, Inc.: New York, 1967; Vol. I, p 481.
(10) Horiike, M.; Oda, J.; Inouye, Y.; Ohno, M. *Agr. Biol. Chem.* **1969**, *33*, 292.
(11) Henry, P. *Jahresber. Fortschr. Chem.* **1889**, 639.
(12) Fischer, E.; Dilthey, A. *Ber.* **1902**, *35*, 848.
(13) Meyer, R.; Bock, A. *Ann.* **1906**, *347*, 98.
(14) Coleman, G. H.; Johnson, H. L. *Inorg. Synth.* **1939**, *1*, 59.
(15) Holmes, B. N. Ph.D Thesis, University of Illinois, 1977.

Scheme II



magnetic resonance for the methyl protons of **3** was shifted upfield by about δ 0.4 from that for the corresponding methyl protons of **10** and by δ 0.25 from the same in **5**. The ^{13}C NMR signal at δ 66.4, which indicated retention of the quaternary carbon, experienced a downfield shift of ~17 ppm from C2 in the precursor, corresponding to the formation of the conjugated system in **3**. The resonance for the methyl carbon experienced an upfield shift of 5.5 ppm in going from **10** to **3**, reflecting, as did the relative resonance values for the methyl protons, the positioning of the methyl group with respect to the near-planar 4-atom system: 5–1–2–3. Compound **3** absorbed UV maximally at 267 nm (ϵ 5750) in distilled water and also at pH 9, whereas the ring was disrupted in pH 4 buffer. In dimethylformamide–water (66%), the observed pH was 8.5 and decomposition took place below pH 5. Aqueous acetic acid destroyed the ring system, as shown by the changes in the ^1H NMR spectrum. Accordingly, it was recognized that final ring closure of **3** to **1** would have to be carried out above pH 5 and preferably under basic conditions.

The final fusion of the pyrimidine ring onto **3** was effected by treatment with formamidine at room temperature. The product obtained was devoid of the characteristic stretching frequency for C≡N in the IR spectrum, indicating that ring closure had occurred. The mass spectra of the product (at 10 and at 70 eV), which exhibited a molecular ion peak at *m/e* 149 (M^+, 100%), and the elemental analyses were in agreement with values for the molecular formula $C_6H_7N_5$. The ^1H NMR spectrum showed two heteroaromatic CH singlets at δ 7.43 and 7.95, NH_2 resonance at 8.01 exchangeable with D_2O, and a singlet for CH_3 at δ 2.25. The pronounced downfield shift of the CH_3 resonance, $\Delta\delta$ 0.67, in going from precursor **3** to product was suggestive not of **1**, but of an isomer that was a methyl-substituted aromatic type. The ^{13}C NMR spectrum of the product provided the decisive answer since it exhibited no signal indicative of the crucial quaternary carbon required by structure **1**, thereby confirming that a cyclization rearrangement had taken place. On the basis of analogy with the cyclization rearrangements that proceed through a 5-substituted guanine intermediate[1-3] and of consistency with the spectroscopic data, the $C_6H_7N_5$ product was considered to be 4-amino-8-methylimidazo[1,5-*a*]-1,3,5-triazine (**11**).

The structure was established as **11** by unequivocal synthesis. 4(5)-Amino-5(4)-methylimidazole was obtained as the dihydrochloride salt by reduction of 5(4)-methyl-4(5)-nitroimidazole with stannous chloride and concentrated hydrochloric acid.[16] The reaction of the free base, 4(5)-amino-5(4)-methylimidazole (**12**), with methyl *N*-cyanomethanimidate (**13**),[17] probably through the intermediate **14** (Scheme II), gave 4-amino-8-methylimidazo-[1,5-*a*]-1,3,5-triazine (**11**) in excellent yield, identical in all respects with the $C_6H_7N_5$ product obtained from 5-amino-4-cyano-4-methyl-4*H*-imidazole (**3**) and formamidine.

MINDO/3 Treatment

Semiempirical molecular orbital calculations using Dewar's MINDO/3 program[18] were performed to determine molecular equilibrium geometries and heats of formation of 5-methyl-5*H*-adenine (**1**), the rearrangement product **11**, and possible intermediates between these. Initial estimates were made for the geometries based on standard bond lengths and angles,[19] e.g.:

Table I. Calculated Parameters for Equilibrium Geometry of 5-Methyl-5*H*-adenine (1)

bond lengths		bond angles		dihedral angles[a]	
coordinate	length, Å	coordinate	angle, deg	coordinate	angle, deg
N10–C6	1.35	N10–C6–N1	115.6	N10–C6–N1–C2	170.2
C6–N1	1.31	C6–N1–C2	122.5	C6–N1–C2–N3	−3.9
N1–C2	1.39	N1–C2–N3	122.2	N1–C2–N3–C4	−8.8
C2–N3	1.31	C2–N3–C4	111.7	C2–N3–C4–N9	233.6
N3–C4	1.37	N3–C4–N9	122.3	N3–C4–N9–C8	169.5
C4–N9	1.30	C4–N9–C8	106.6	C4–N9–C8–N7	−5.8
N9–C8	1.41	N9–C8–N7	113.0	N9–C8–N7–C5	11.5
C8–N7	1.30	C8–N7–C5	109.8	C8–N7–C5–C11	112.3
N7–C5	1.47				
C5–C4	1.57				
C5–C6	1.56				
C5–C11	1.56				

[a] The following convention was used in defining dihedral angle: for the four atoms A–B–C–D, one looks along the C–B axis from C toward B, then rotates the A–B bond clockwise about the B–C axis until it eclipses the C–D bond. The angle of rotation is the dihedral angle. Negative angles correspond to counterclockwise rotations.

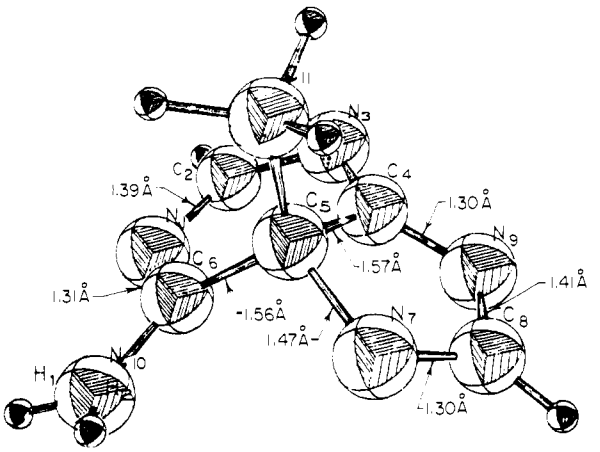


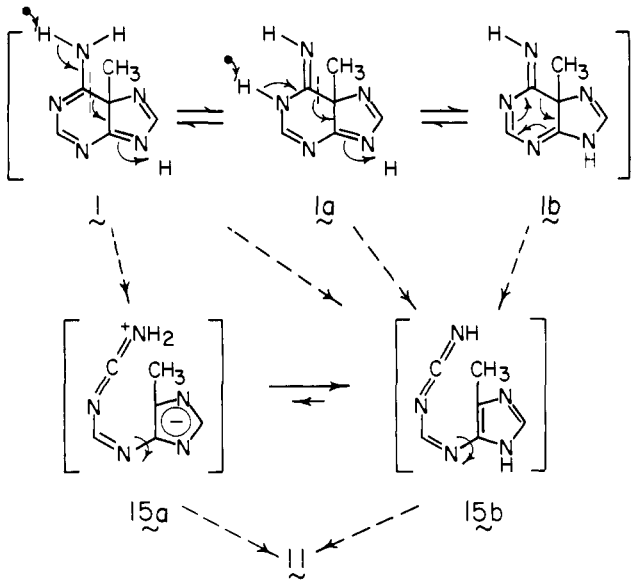
Figure 1. ORTEP view of 5-methyl-5*H*-adenine (**1**) (MINDO/3).

C—N, 1.37 Å; C=N (6-membered ring), 1.28; C—N (6-membered ring), 1.37; C=N (5-membered ring), 1.31; C—N (5-membered ring), 1.39; C—N (to 4° carbon), 1.47; $C(sp^3)$—$C(sp^3)$, 1.54; $C(sp^3)$—$C(sp^2)$, 1.51. The N–H, C–H (ring), and C–H (methyl) bond lengths were fixed at 0.98, 0.95, and 1.1 Å, respectively.[19] Tetrahedral geometry was first assumed for the angular quaternary carbon and for the methyl group in **1** and a pyramidal structure for the NH_2 function. The equilibrium geometry was found by minimizing energy with respect to all parameters except C–H and N–H bond lengths. The final optimized parameters are summarized in Table I, and the calculated geometry is presented in Figure 1.

The strained nature of the molecule was reflected in the results of the calculations. Of particular interest is the considerable deviation from planarity. The presence of the quaternary carbon at the ring junction (Figure 1) forces other parts of the molecule into a puckered conformation that appears to diminish conjugation in the molecule. The alternating long and short bonds reflect reduced conjugation or the absence of conjugation between the double bonds. The calculated values of the two ring-carbon bonds

(16) Weidenhagen, R. Herrmann, R. *Ber.* **1935**, *68*, 2205.
(17) Hosmane, R. S.; Leonard, N. *J. J. Org. Chem.* **1981**, *46*, 1457.
(18) Bingham, R. J. S.; Dewar, M. J. S.; Lo, D. H. *J. Am. Chem. Soc.* **1975**, *97*, 1285.
(19) (a) "Tables of Interatomic Distances in Molecules and Ions"; The Chemical Society, London, 1965; (b) Some of the values are taken from X-ray crystallographic measurements on imidazo[1,5-*a*]-1,3,5-triazinones (ref 2, Supplementary Material).
(20) Cox, J. D.; Pilcher, G. "Thermochemistry of Organic and Organometallic Compounds"; Academic Press: London, 1970; p 158.
(21) This investigation.
(22) See also formula **5** and footnote 5 in ref 3.

Scheme III



to the quaternary carbon, C5–C4 and C5–C6, are longer than normal: 1.57 and 1.56 Å, respectively, vs. the standard value for a $C(sp^3)$–$C(sp^2)$ bond, 1.51 Å. The calculated value for the heat of formation, $\Delta H_f°$, of compound **1** (exo-NH_2 tautomer) is 94.5 kcal mol^{-1}, a value which is very high for a molecule of this size (cf. 71.1 kcal mol^{-1} for 1,3,5,7-cyclooctatetraene).[20] The calculated value for the heat of formation of structure **11** is 42.6 kcal mol^{-1}, indicating the much greater stability of the rearranged product with respect to a transient intermediate such as **1**. In the hypothetical 5-methyl-5*H*-adenine (Figure 1), the most likely candidates for bond breaking are the extended C5–C4 and C5–C6 bonds. Of the two possibilities, the former would lead to a 9-membered ring of at least the same degree of instability as **1**. Cleavage of the C5–C6 bond would lead to a more stable intermediate containing an aromatic imidazole ring and a carbodiimide side chain, as in **15**. Structure **15a** would result from heterolytic bond scission in **1**, while **15b** would result from electrocyclic bond cleavage (in tautomer **1b**, for which the calculated $\Delta H_f°$ value is 84.0 kcal mol^{-1}). The calculated value for the heat of formation of intermediate **15b** is 63.2 kcal mol^{-1}, which places it logically on the route from **1** to **11**. Simple rotation about the exocyclic C–N bond orients the carbodiimide function in juxtaposition to the imidazole N–H for ring reclosure (→**11**). Under the neutral conditions of the rearrangement of **3** + formamidine in ethanol to give **11**, it is unlikely that the conjugate anion of **1** (or its tautomeric forms) would be produced; moreover, our calculations show the related anion to have a heat of formation about as great as that of **1**. Nevertheless, it is possible that in the course of proton transfer, as in the tautomerization process, C5–C6 bond cleavage could occur (**1** → **15b** ← **1a** in Scheme III), leading, by general acid–base catalysis, to the same intermediate as obtainable electrocyclically from tautomer **1b**. Yet another possibility for the **1** → **11** conversion, involving two successive [1,5] sigmatropic shifts and a spiro intermediate, can be discarded because the intermediate (not shown) is only slightly more stable (calculated $\Delta H_f° = 88.1$ kcal mol^{-1}) than **1**.

Finally, a close inspection of the rearrangement of **3** to **11** in the reaction with formamidine reveals the unique property that the C≡N group at the 4-position of compound **3** has been translocated efficiently and with ease to the ring nitrogen two atoms removed, where it becomes attached as a $\gtrdot CNH_2$ function (see boxed moieties in Scheme I). While we favor an intramolecular route, proceeding through **1** and **15**, we have not fully eliminated intermolecular processes from consideration, including those that would involve initial C4–CN bond cleavage. Since the bridgehead-substituted purine ring system, whether approached via ring closure of either the imidazole (**4**)[1-3] or the pyrimidine (**3**),[21] leads to the same type of imidazotriazine rearrangement product, our conclusion is that the transient intermediacy of a 5-substituted 5*H*-purine provides the best explanation for the observations.[22] We anticipate finding generality within the category of translocative rearrangements.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM-390 spectrometer, and ^{13}C NMR spectra were obtained on a Jeol FX-60 fourier transform instrument operating at 15.03 MHz. Both are reported in ppm using tetramethylsilane as an internal reference standard. Ultraviolet absorption spectra were measured on a Beckman Acta MVI spectrophotometer. Mass spectra were run on a Varian MAT CH-5 instrument coupled with a 620i computer and a STATOS recorder. Infrared spectra were obtained on a Perkin-Elmer 337 spectrophotometer. Microanalyses were performed by Mr. Josef Nemeth and his staff. The MINDO/3 calculations were performed on the Vax/VMS computer in the School of Chemical Sciences of the University of Illinois.

Methylmalonamide. A solution of diethyl methylmalonate (16 mL, 93 mmol) in 60 mL of CH_3OH was saturated with anhydrous NH_3 at 0 °C and heated in a steel bomb at 110 °C for 16 h. The NH_3 was evaporated on a steam bath, and the solid was filtered in vacuo and recrystallized from EtOH–H_2O as colorless crystals (10.6 g, 98%): mp 208–210 °C (lit.[12] mp 216.5 °C (corrected)).

Methylmalononitrile (6). Methylmalonamide (9.0 g, 78 mmol) was mixed thoroughly with P_2O_5 (18 g, 127 mmol) and the mixture was heated gently in vacuo (3 mmHg) in a Claisen distillation flask attached to a receiver immersed in dry ice. The product distilled (60–70 °C) as a colorless liquid which solidified as long, colorless needles of **6** (4.65 g, 75%): mp 32–34 °C (lit.[11] mp 26.2 °C).

2-Amino-2-cyanopropionitrile (5). In a dry three-necked flask fitted with a N_2 inlet, an addition funnel, and a reflux condenser was placed a slurry of NaH (prewashed three times with dry toluene to remove adhering oil) (1.92 g, 80 mmol) in dry THF (50 mL). A solution of methylmalononitrile (**6**) (5.6 g, 70 mmol) in 50 mL of dry THF was added slowly drop by drop through the addition funnel, while the mixture was stirred with a magnetic stirrer and cooled as necessary. The mixture (containing **7**) was stirred at room temperature under N_2 for an additional 2-h period. Then a cold, ethereal solution of chloramine[14] (80 mmol) in 200mL of ether was added through the top of the condenser approximately 2 mL at a time. The addition took about 2 h. The mixture was stirred at 20 °C overnight and the yellow precipitate was filtered. The filtrate was evaporated to dryness on a rotary evaporator using a water bath, the temperature of which did not exceed 40 °C. Approximately 200 mL of ether was added to the residue, any precipitate formed was separated by filtration, and the filtrate was again evaporated to dryness, this time with drying over anhydrous Na_2SO_4 for several hours, to obtain an oil that was used directly for the next stage in the reaction sequence (**5**, 4.12 g, 62%). An analytical sample of **5** was prepared by distilling a small amount in a Kügelrohr apparatus (85–90 °C, 1.8 mm) as a colorless oil which became yellowish upon exposure to air; ^1H NMR ($(CD_3)_2SO$) δ 1.85 (s, 3, CH_3), 3.65 (s, 2, NH_2, exchangeable with D_2O); ^{13}C NMR ($(CD_3)_2SO$) δ 26.18 (CH_3), 43.3 (quaternary C), 118.1 (C≡N); IR (neat) 3375, 3300 (NH), 2250 (C≡N) cm^{-1}; mass spectrum (10 and 70 eV) *m/e* 95 (M^+), 80 ($M^+ - CH_3$), 69 ($M^+ - CN$), 53 ($M^+ - CH_3 - HCN$).

Anal. Calcd for $C_4H_5N_3$: C, 50.51; H, 5.30; N, 44.19. Found: C, 50.35; H, 5.42; N, 43.96.

2-Amino-2-cyanopropionitrile *p*-toluenesulfonate (8) was prepared by adding 2.0 g of *p*-toluenesulfonic acid monohydrate (10.5 mmol) to 1.0 g of **5** (10.5 mmol) in 10 mL of ether and stirring the mixture for 5 min with a magnetic stirrer at 20 °C. The precipitate was filtered in vacuo and recrystallized from acetonitrile as colorless flakes (2.5 g, 83%): mp 165–167 °C dec; ^1H NMR ($(CD_3)_2SO$) δ 1.95 (s, 3, aliphatic CH_3), 2.28 (s, 3, aromatic CH_3), 7.05 (d, 2, J = 8.0 Hz, aromatic CH's), 7.45 (d, 2, J = 8.0 Hz, aromatic CH's), 7.72 (s, 3, $-NH_3^+$, exchangeable with D_2O).

Anal. Calcd for $C_{11}H_{13}N_3O_3S$: C, 49.43; H, 4.90; N, 15.72. Found: C, 49.43; H, 4.95; N, 15.83.

2-Acetamido-2-cyanopropionitrile (9). A mixture of 2-amino-2-cyanopropionitrile (**5**) (300 mg, 3.2 mmol) and Ac_2O (6.0 mL, 64 mmol) was heated under reflux for 3 h with protection from atmospheric moisture. The solution was evaporated to dryness on a rotary evaporator using a hot-water bath to obtain a solid which was recrystallized from water as colorless needles of **9** (390 mg, 89%): mp 160–161 °C; ^1H NMR ($(CD_3)_2SO$) δ 1.99 (s, 3, quaternary CH_3), 2.02 (s, 3, amide CH_3), 9.43 (s, 1, NH, exchangeable with D_2O); IR (KBr) 3240 (NH), 1675 (C=O) cm^{-1}; mass spectrum (10 and 70 eV) *m/e* 137 (M^+), 122 ($M^+ - CH_3$), 95 ($M^+ - CH_3 - HCN$), 79 ($M^+ - CH_3 - COCH_3$).

Anal. Calcd for $C_6H_7N_3O$: C, 52.54; H, 5.15; N, 30.64. Found: C, 52.41; H, 5.07; N, 30.94.

2-Cyano-2-(methoxymethyleneamino)propionitrile (10) and 2-Cyano-2-(methoxymethyleneamino)propionamide. In a dry, 100-mL, three-necked flask, equipped with a magnetic stirrer, N_2 inlet, and a reflux condenser, were placed 2-amino-2-cyanopropionitrile (**2**) (3.5 g, 37 mmol) and trimethyl orthoformate (75 mL, 685 mmol). The mixture was stirred at 20 °C under N_2 for 5 min. Then, formic acid (1.0 mL, 26.4 mmol) was added in one lot through the top of the condenser, and the mixture was refluxed on a heating mantle for 3 h. The mixture was evaporated on a rotary evaporator using a water bath maintained at 40 °C. The residual oil was mixed with 5 mL of dry toluene and the mixture was again evaporated. A small quantity of solid that separated from the oil was filtered, using dry toluene as a wash, and was recrystallized from chloroform–ligroin as colorless needles of the amide (0.20 g, 3.5%): mp 130–131 °C; ^1H NMR ($(CD_3)_2SO$) δ 1.68 (s, 3, C–CH_3), 3.78 (s, 3, O–CH_3), 7.34 (broad, 1, amide N–H, exchangeable with D_2O), 7.68 (broad, 1, amide N–H, exchangeable with D_2O), 7.93 (s, 1, CH); IR (KBr) 3420 (NH), 1705 (C=O) cm^{-1}; mass spectrum (10 and 70 eV) m/e 112 (M^+ – HNCO), 97 (M^+ – HNCO – CH_3), 85 (M^+ – HNCO – HCN).

Anal. Calcd for $C_6H_9N_3O_2$: C, 46.44; H, 5.85; N, 27.08. Found: C, 46.63; H, 5.90; N, 27.00.

The toluene filtrate after separation of the solid was evaporated to dryness on a rotary evaporator, and the residual oil was distilled in a Kügelrohr apparatus (oven temperature 75–85 °C (2 mm)) to obtain a colorless oil (3.6 g, 71%): ^1H NMR ($(CD_3)_2SO$) δ 2.0 (s, 3, C–CH_3), 3.73 (s, 3, O–CH_3), 8.1 (s, 1, CH); ^{13}C NMR ($(CD_3)_2SO$) δ 28.24 (C–CH_3), 50.0 (quaternary C), 54.59 (O–CH_3), 115.79 (C≡N), 161.88 (N=CH); IR (neat) 3010 (=CH), 2950 (CH_3), 1650 (N=C) cm^{-1}; mass spectrum (10 and 70 eV) m/e 137 (M^+), 122 (M^+ – CH_3).

Anal. Calcd for $C_6H_7N_3O$: C, 52.55; H, 5.15; N, 30.64. Found: C, 52.71; H, 5.14; N, 30.88.

5-Amino-4-cyano-4-methyl-4*H*-imidazole (3). A solution of 2-cyano-2-(methoxymethyleneamino)propionitrile (**10**) (0.40 g, 2.9 mmol) and 2-propanol saturated with NH_3 at 0 °C (25 mL) was stirred at 0 °C in a stoppered vessel for 18 h. The orange solution was evaporated to dryness, the residue was triturated with ether, and the solid was filtered in vacuo and recrystallized from dioxane as colorless crystals of **4** (0.25 g, 70%): mp >300 °C; ^1H NMR ($(CD_3)_2SO$) δ 1.58 (s, 3, CH_3), 7.6 (s, 1, CH), 8.45 (broad, 2, NH_2, exchangeable with D_2O); ^{13}C NMR ($(CD_3)_2SO$) δ 22.5 (CH_3), 66.4 (4-C), 117.6 (C≡N), 170.1 (2-C), 184 (5-C); UV (H_2O) λ_{max} 267 nm (ϵ = 5750); IR (KBr) 3200 (NH), 2250 (C≡N) cm^{-1}; mass spectrum (10 and 70 eV) m/e 122 (M^+), 95 (M^+ – HCN), 80 (M^+ – CH_3 – HCN).

Anal. Calcd for $C_5H_6N_4$: C, 49.17; H, 4.95; N, 45.88. Found: C, 49.22; H, 4.75; N, 45.94.

Reaction of 5-Amino-4-cyano-4-methyl-4*H*-imidazole (3) with Ammonia. A mixture of **3** (40 mg, 0.33 mmol) and 2-propanol (40 mL) saturated with NH_3 at 0 °C was stirred in a steel bomb at room temperature for 15 min. The mixture was evaporated to dryness at 40 °C to obtain a solid (50 mg); ^1H NMR ($(CD_3)_2SO$) δ –0.2 (br, 9, 3 NH_3, exchangeable with D_2O), 1.63 (s, 3, CH_3), 7.9 (s, 1, CH), 8.83 (broad, 2, NH_2, exchangeable with D_2O); IR (KBr) 3600–2500 (broad), 2250 (C≡N) cm^{-1}.

A mixture of this solid (30 mg) and silica gel (Brinkman grade 0.05–0.2 mm) in absolute ethanol (10 mL) was stirred for 2 min. The mixture was filtered in vacuo, and the filtrate was evaporated to dryness. The ^1H NMR of the residue was identical with that of the free base **3**.

4-Amino-8-methylimidazo[1,5-*a*]-1,3,5-triazine (11). Method A: A mixture of 5-amino-4-cyano-4-methyl-4*H*-imidazole (**3**) (122 mg, 1mmol), formamidine acetate (115 mg, 1.1 mmol), and absolute ethanol (12 mL) was stirred under nitrogen at 20 °C for 1 h to form a clear solution. A solution resulting from sodium (23 mg, 1 mg-atom) dissolved in absolute ethanol (4 mL) was introduced dropwise through a hypodermic syringe. The mixture was stirred at ambient temperature for an additional 7 h (shorter time was satisfactory) and evaporated to dryness on a rotary evaporator at 20 °C, and the residue was dissolved in 5 mL of H_2O. The pH was adjusted to 6 with glacial acetic acid, and the solution was cooled in an ice bath. The solid that separated was recrystallized from H_2O as colorless needles of **11** (130 mg, 87%); mp >300 °C; ^1H NMR ($(CD_3)_2SO$) δ 2.25 (s, 3, CH_3), 7.43 (s, 1, 2-H), 7.95 (s, 1, 6-H), 8.01 (br, 2, NH_2, exchangeable with D_2O); ^{13}C NMR ($(CD_3)_2SO$) δ 11.6 (CH_3), 121.3 (2-C), 123.8 (8-C), 133.7 (8a-C), 148.4 (4-C), 149.4 (6-C); IR (KBr) 3400–2800 (br, NH) cm^{-1}; MS (70 eV) m/e (relative intensity) 149 (M^+, 100), 122 (M^+ – HCN, 26), 107 (M^+ – HCN – CH_3, 17), 96 (10), 80 (18), 53 (24), 43 (39), 28 (27).

Anal. Calcd for $C_6H_7N_5$: C, 48.31; H, 4.73; N, 46.96. Found: C, 48.30; H, 4.66; N, 47.04.

Method B: Structure Proof by Synthesis. A 25-mL, three-necked flask, equipped with a reflux condenser, N_2 inlet, serum cap, and magnetic stirrer, was charged with 4(5)-amino-5(4)-methylimidazole (**12**) dihydrochloride[16] (170 mg, 1 mmol), $NaOCH_3$ (108 mg, 2 mmol), and absolute MeOH (8 mL). The mixture was stirred under nitrogen to form a clear solution. Methyl *N*-cyanomethanimidate (**13**)[17] (110 mg, 1.31 mmol) dissolved in 5 mL of absolute MeOH was introduced through a hypodermic syringe and the solution was refluxed for 2.5 h. The mixture was evaporated to dryness. The residue was dissolved in 5 mL of H_2O, neutralized with glacial acetic acid, and cooled in an ice bath. The precipitated solid was filtered in vacuo and recrystallized from H_2O as colorless needles (122 mg, 82%): mp >300 °C.

^1H NMR, IR, and mass spectral data as well as the TLC behavior of this compound were identical with those of product **11** obtained by method A.

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