Rearrangements in Heterocyclic Synthesis. 2. Novel Transformations of 2-Aminonicotinonitrile and Anthranilonitrile

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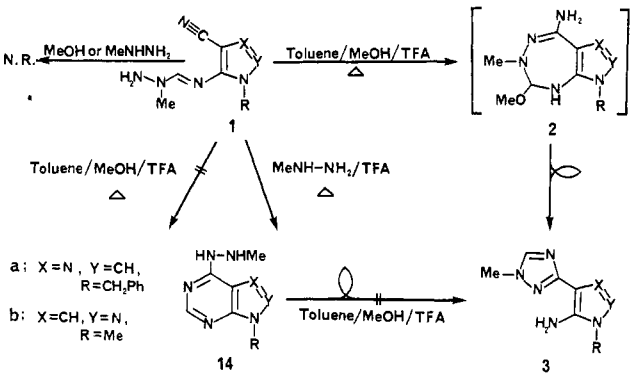
Methyl *N*-(3-cyanopyridin-2-yl)methanimidate (**4**) was prepared by the reaction of 2-aminonicotinonitrile with trimethyl orthoformate, catalyzed by trifluoroacetic acid. Treatment of **4** with methylhydrazine at 0 °C provided *N*-amino-*N*-methyl-*N'*-(3-cyanopyridin-2-yl)formamidine (**5a**) as a mixture of cis and trans isomers, while the same reaction at room temperature yielded 4-(β-methylhydrazino)pyrido[2,3-*d*]pyrimidine (**6**). Thermolysis of **5a** or **6** in refluxing toluene–methanol, catalyzed by trifluoroacetic acid, yielded 2-amino-3-(1-methyl-1,2,4-triazol-3-yl)pyridine (**8**). A tentative mechanism for the conversion **5a** → **6** → **8** has been proposed (Scheme IV). An alternative reaction pathway (Scheme V) was eliminated by the ^{15}N labeling studies (Scheme VI). The translocative rearrangement of the vinylogous cyano hydrazidines of imidazole (**1a**) and of pyrazole (**1b**) to the respective 3-(5-aminoimidazol-4-yl)-1,2,4-triazole (**3a**) and 3-(5-aminopyrazol-4-yl)-1,2,4-triazole (**3b**) failed to show evidence for the intermediacy of the corresponding 6-hydrazinopurine (**14a**) and 4-hydrazinopyrazolo-[3,4-*d*]pyrimidine (**14b**). Methyl *N*-(2-cyanophenyl)methanimidate (**15**), prepared from anthranilonitrile, yielded 4-(β-methylhydrazino)quinazoline (**16**) upon reaction with methylhydrazine. Compound **16** underwent thermolysis in toluene–methanol–TFA to give 1-methyl-3-(2-aminophenyl)-1,2,4-triazole (**17**). Structures of compounds **6**, **8**·TFA, and **14b** were established by single-crystal X-ray analyses.

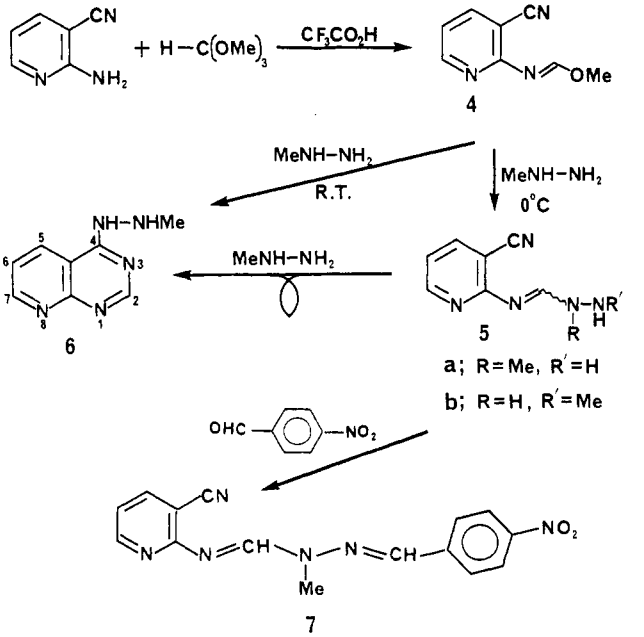
We have recently described[1] a novel "translocative" rearrangement[2] of the vinylogous cyano–hydrazidines of imidazole and pyrazole systems (**1**) to the corresponding triazole derivatives (**3**) via the proposed intermediate **2** (Scheme I). In this paper, we further demonstrate the applicability of this rearrangement to the analogous six-membered-ring systems, both heterocyclic and carbocyclic, and also present additional data pertaining to the mechanism of this rearrangement. Our findings indicate that the rearrangement proceeds through different pathways for the five- and six-membered-ring systems. The course of this endeavor has also led us to discover new heterocyclic transformations which carry implications of broad synthetic utility.

Our present studies began with the reagent methyl *N*-(3-cyanopyridin-2-yl)methanimidate (**4**) (Scheme II), which was prepared by reaction of 2-aminonicotinonitrile[3] with trimethyl orthoformate, catalyzed by trifluoroacetic acid. Treatment of **4** with 1 equiv of methylhydrazine at 0 °C provided *N*-amino-*N*-methyl-*N'*-(3-cyanopyridin-2-yl)formamidine (**5a**) as a 1:1 mixture of cis and trans isomers, while the same reaction with a slight excess of methylhydrazine at room temperature yielded 4-(β-methylhydrazino)pyrido[2,3-*d*]pyrimidine (**6**). The intermediacy of **5a** in the conversion **4** → **6** was confirmed by a separate reaction of **5a** with methylhydrazine, which gave **6** exclusively. Structure **6** was confirmed by single-crystal X-ray analysis (Figure 1), while structure **5a** was distinguished from the alternative **5b** by the ^1H NMR spectrum of the product, which exhibited singlets for both Me and NH_2. The above observation was also consistent with the known reactivity of methylhydrazine, which is reported to react with electrophiles from its methyl end.[1,4,5] Finally, structure **5a** was confirmed by conversion to the corresponding *p*-nitrobenzaldehyde hydrazone derivative (**7**).

Scheme I



Scheme II



(1) Hosmane, R. S.; Lim, B. B.; Burnett, F. N. *J. Org. Chem.* **1988**, *53*, 382.

(2) The term "translocative rearrangement" has been employed to describe the transfer of a functional group from one location of the molecule to the other. For earlier examples, see: (a) Hosmane, R. S.; Bakthavachalam, V.; Leonard, N. J. *J. Am. Chem. Soc.* **1982**, *104*, 235. (b) Balicki, R.; Hosmane, R. S.; Leonard, N. J. *J. Org. Chem.* **1983**, *48*, 3.

(3) Taylor, E. C., Jr.; Crovetti, A. J. *J. Org. Chem.* **1954**, *19*, 1633.

(4) Leiby, R. W.; Heindel, N. D. *J. Org. Chem.* **1976**, *41*, 2736.

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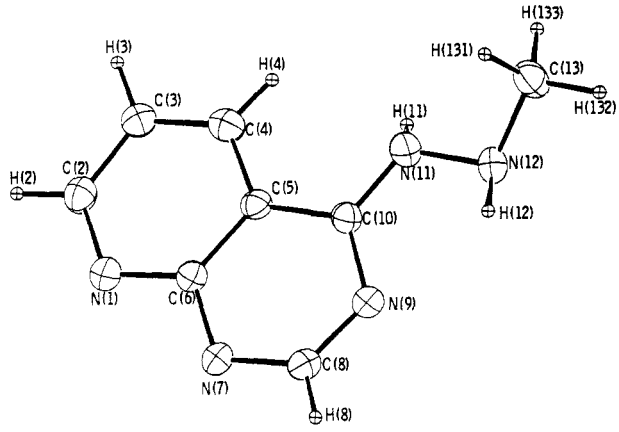
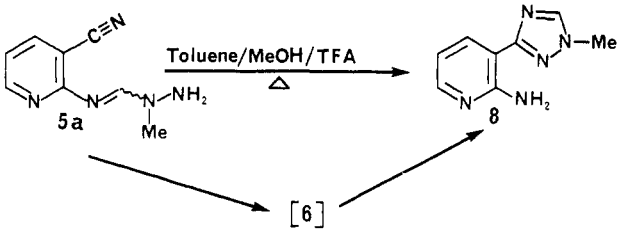


Figure 1. ORTEP view of **6** showing the atom numbering scheme and thermal ellipsoids at the 30% probability level.

Scheme III



Preparation of a similar hydrazone derivative is precedented to facilitate assigning the correct isomeric form for the product of reaction of methylhydrazine with phenylacetic anhydride.[6]

When compound **5a** or **6** was subjected to the "translocative" rearrangement[1,2] either independently or as a mixture, under conditions employed for the five-membered-ring heterocycles,[1] using toluene–methanol–trifluoroacetic acid, the product 2-amino-3-(1-methyl-1,2,4-triazol-3-yl)pyridine (**8**) was isolated in nearly quantitative yields (Scheme III). Compound **6** was detected as an intermediate during the separate conversion **5a** → **8**. In fact, the transformation of **5a** into **6** was so facile that an attempted separation of two geometric isomers of **5a** by flash chromatography on a silica gel column resulted in the quantitative isolation of **6**. Compound **6** was also formed when a solution of **5a** in methanol or water was allowed to stand at room temperature for several hours. On the other hand, both **6** and **8** were detected by TLC when an aqueous solution of **5a** was stirred at room temperature with silica gel or with catalytic amounts of trifluoroacetic acid. Structure **8** (as its TFA salt) was confirmed by single-crystal X-ray analysis (Figure 2).

The following tentative mechanism is proposed for the conversion of **5a** into **6** by nucleophiles methylhydrazine, methanol, or water and for the subsequent acid-catalyzed rearrangement of **6** to the final product **8** (Scheme IV). An alternative pathway for the conversion **5a** → **6** invoking nucleophilic attack at the nitrile function of **5a** was considered less likely in view of the failed reactions of either nicotinonitrile or 2-aminonicotinonitrile with methylhydrazine at reflux overnight. Likewise, another mechanism, for the conversion **5a** → **8**, involving a spiro intermediate **9** (Scheme V),[7] was eliminated by the following

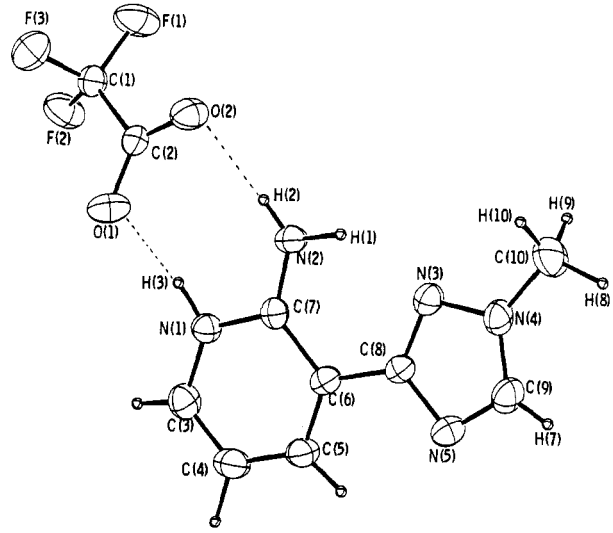


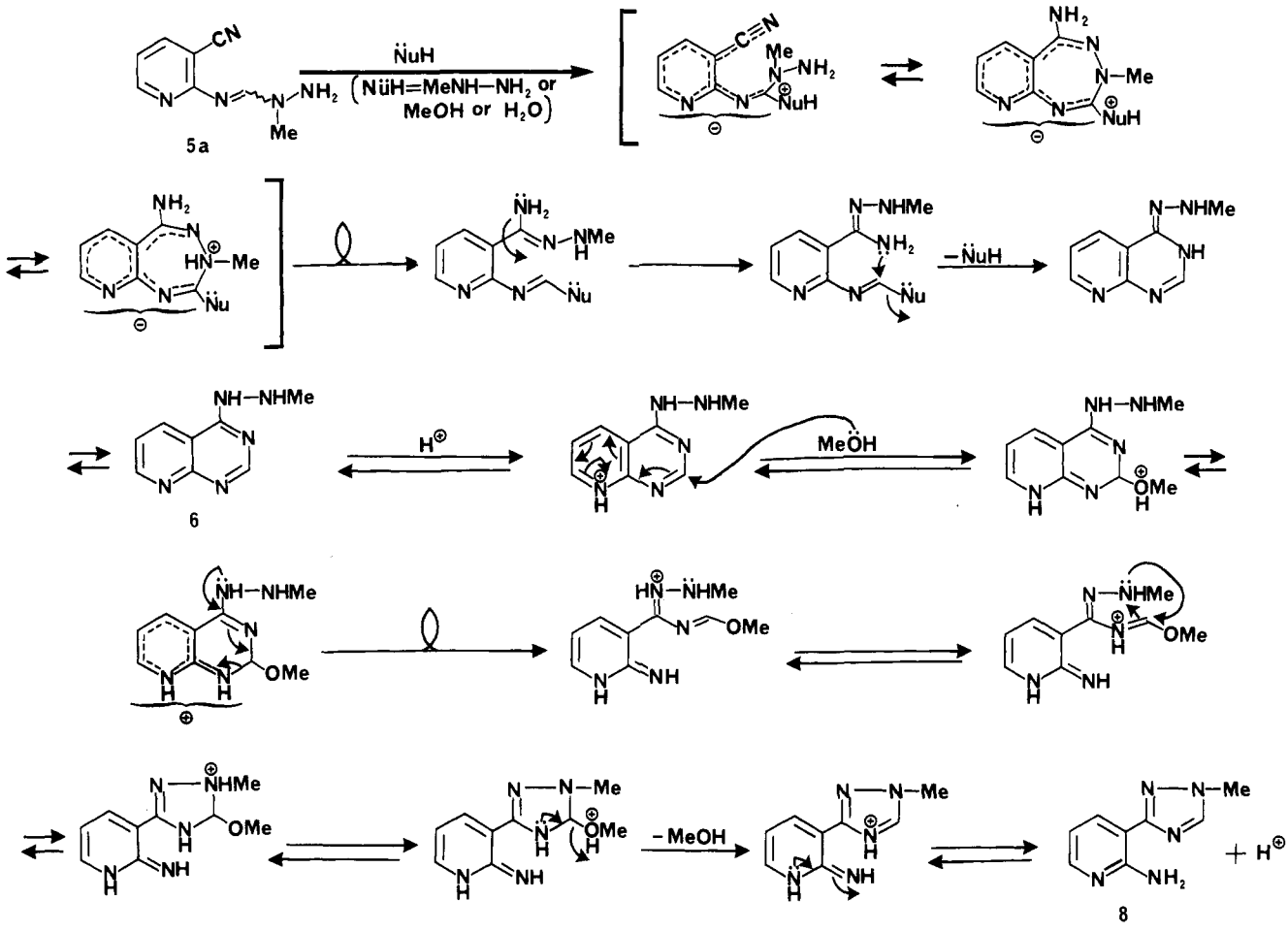
Figure 2. ORTEP view of $8 \cdot CF_3CO_2H$ showing the atom numbering scheme and thermal ellipsoids at the 30% probability level.

labeling experiments (Scheme VI). The ^{15}N-labeled 2-aminonicotinonitrile (**10**) was prepared by reaction of 2-chloro-3-cyanopyridine with [^{15}N]ammonia (17% enriched). Compound **10** was carried through the reaction sequences of Schemes II and III to obtain the labeled rearrangement product **12** or **13** depending upon whether the rearrangement proceeded through Scheme IV or Scheme V. The structural distinction between **12** and **13** was made by using ^1H and ^{15}N NMR. The ^1H NMR spectrum of the rearranged product in deuteriated dimethyl sulfoxide–TMS (Figure 3a) showed a sharp doublet (δ 7.02) with a large coupling constant, corresponding to the $^{15}NH_2$ group ($J_{^{15}NH}$ = 88.0 Hz). The observed chemical shift and coupling constant are in the range expected of a pyramidal nitrogen–proton bonding.[8] The doublet was spaced equally on either side of a broad singlet at δ 7.02 corresponding to the unlabeled NH_2. Both the doublet and the singlet were exchangeable with D_2O. The percent ratio of peak intensities, doublet/(doublet + singlet), was ≈17, which was consistent with the percent isotopic enrichment of the ammonia gas employed for the reaction. The ^1H NMR spectrum of the starting material **10** (Figure 3b) showed a similar spectral pattern for the $^{15}NH_2$ function by exhibiting a doublet and a singlet centered at δ 6.83 with a comparable coupling constant ($J_{^{15}NH}$ = 88.6 Hz) and a ratio of isotopic enrichment ≈17%. Thus, the extranuclear NH_2 group of **10** is retained through the rearrangement, as in **12**. By contrast, no such one-bond ^{15}N–^1H coupling would be possible in structure **13**. The ^{15}N NMR spectra of **10** and **12** corroborated the above structural distinctions achieved by ^1H NMR. A 51-MHz ^{15}N NMR spectrum of the final product (Figure 3c) in deuteriated dimethyl sulfoxide (taken with nitromethane as an external reference standard and with chemical shifts converted to the liquid ammonia scale, δ 0) revealed a triplet in the ^1H-coupled spectrum ($J_{^{15}NH}$ ≈ 88 Hz) or an inverted singlet in the wide-band ^1H-decoupled spectrum at δ 76.5. The ^{15}N signals for the amino group in **10** (Figure 3d) were very similar to those in Figure 3c with respect to both chemical shift (δ 80.8) and coupling constant ($J_{^{15}NH}$ = 89 Hz). Thus, the reaction pathway for the rearrangement is consistent with Scheme IV rather than Scheme V as suggested.[7]

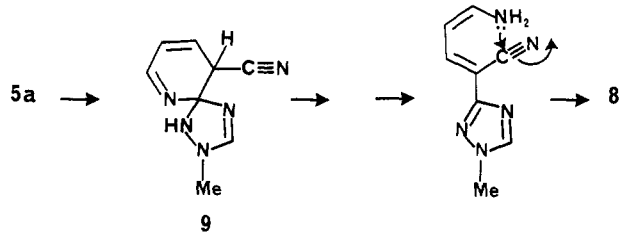
The intermediacy of **6** in the translocative rearrangement **5a** → **8** raised speculations about the involvement

(5) Sunder, S.; Peet, N. P.; Trepanier, D. L. *J. Org. Chem.* **1976**, *41*, 2732.
(6) Theuer, W. J.; Moore, J. A. *J. Org. Chem.* **1964**, *29*, 3734.
(7) The mechanism shown in Scheme V was suggested by one of the reviewers.
(8) Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*; Wiley: New York, 1979; pp 81, 109.

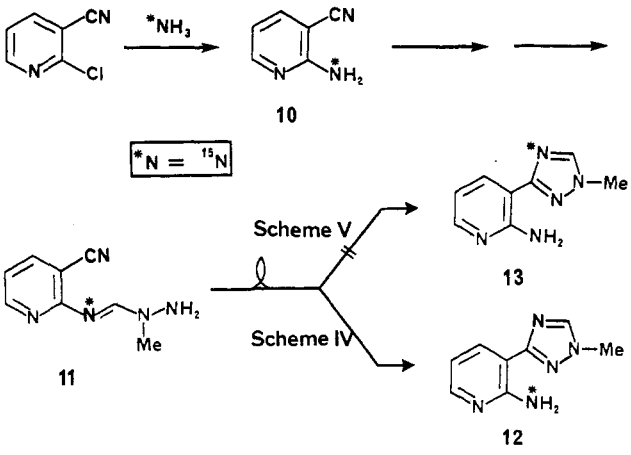
Scheme IV



Scheme V



Scheme VI



of a similar intermediate (viz., 14 in Scheme I) in the rearrangement of 1 to 3[1] as well. This speculation was consistent with the known precedents for the transformation of compounds of type 14 into those of type 3 under acidic reaction conditions,[9] albeit using more drastic conditions (1 N HCl, 7 days!) than those used by us.[1] Nevertheless, a reinvestigation of the conversion 1 → 3 was undertaken. While compound 1, unlike **5a**, failed to react with water, methanol, or methylhydrazine at room temperature in the absence of acid, reaction of 1 with excess methylhydrazine, under acid catalysis, did afford 14 (Scheme I). Structure **14b** was confirmed by X-ray analysis (Figure 4). Regardless, all our efforts to either isolate or detect 14 in the translocative rearrangement of 1 to 3, employing toluene–methanol–TFA, were fruitless in spite of careful monitoring of the reaction at frequent intervals. Compound 14 also failed to rearrange to 3 upon thermolysis in toluene–methanol–TFA under identical conditions employed for the conversion 1 → 3.[1] The starting material 14 was recovered unchanged even after a 7-day period. Thus, the suggested[1] transformation, 1 → 2 → 3, without the intermediacy of 14 still remains a possibility. In this context, it is to be noted that the formation of imidazolyltriazole derivatives such as **3a** from the corresponding 1-aminopurine 9-ribosides has been proposed to proceed through a seven-membered-ring intermediate analogous to **2a** without recourse to the intermediate Dimroth rearrangement product of type 14.[10]

The above results point to two different mechanisms for the translocative rearrangements of five- and six-mem-

(9) Temple, C., Jr.; Kussner, C. L.; Montgomery, J. A. *J. Org. Chem.* **1965**, *30*, 3601.

(10) Huang, G.-F.; Okamoto, T.; Maeda, M.; Kawazoe, Y. *Chem. Pharm. Bull.* **1974**, *22*, 1938. (b) Huang, G.-F.; Maeda, M.; Okamoto, T.; Kawazoe, Y. *Tetrahedron* **1975**, *31*, 1363.

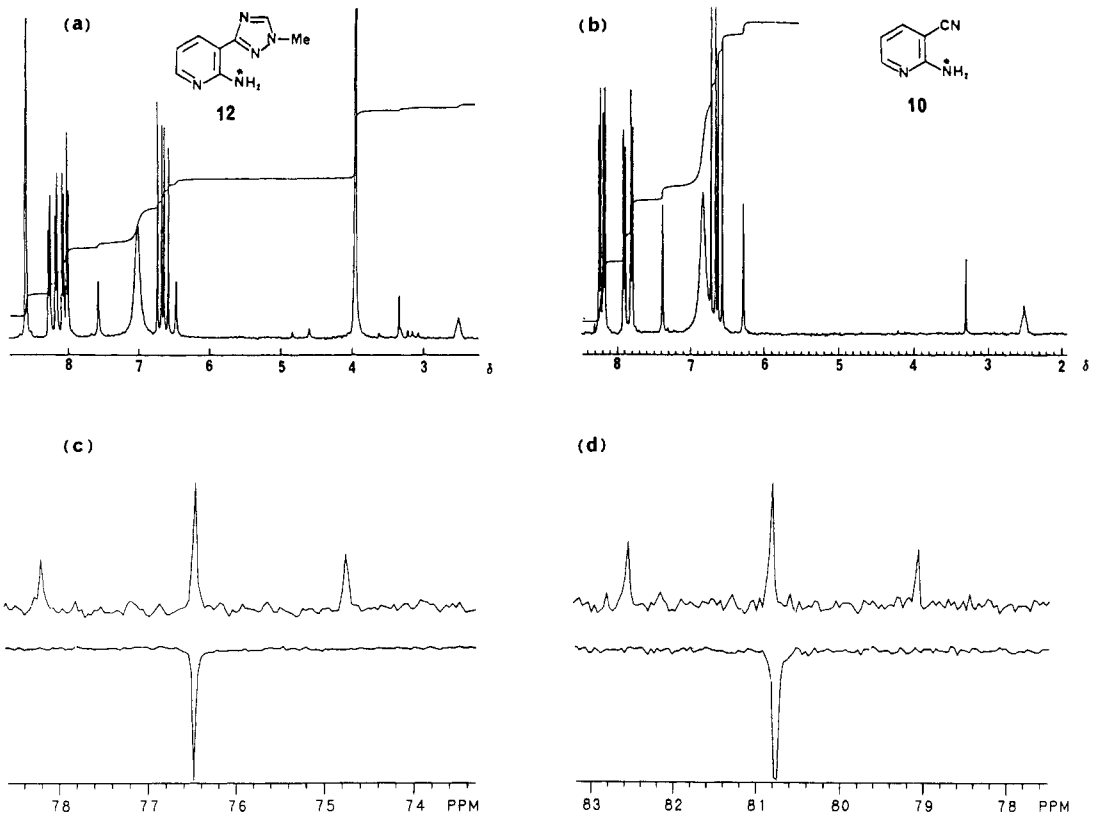


Figure 3. (a) The ^1H NMR spectrum of compound **12** (80 MHz) in Me_2SO-d_6. (b) The ^1H NMR spectrum of compound **10** (80 MHz) in Me_2SO-d_6. (c) The ^{15}N NMR spectrum of **12** (51 MHz) in Me_2SO-d_6. (d) The ^{15}N NMR spectrum of **10** (51 MHz) in Me_2SO-d_6.

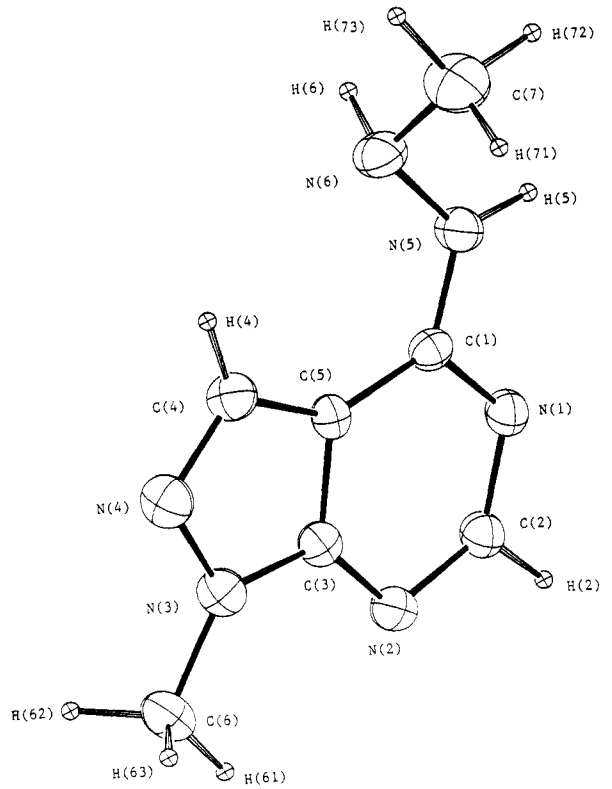
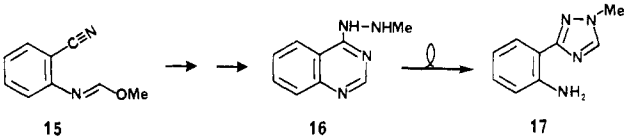


Figure 4. ORTEP view of **14b** showing the atom numbering scheme and thermal ellipsoids at the 30% probability level.

bered-ring heterocycles. Furthermore, within the same family, the course of the rearrangement is also dependent, to a certain extent, upon the nucleophiles employed. These findings are not totally surprising in view of the π-richness of five-membered-ring heterocycles in contrast with the π-deficiency of those with six-membered rings. Thus, the inactivity of **1** toward methanol, water, or methylhydrazine in the absence of acid catalysis can be attributed to the lack of assistance by the π-rich imidazole in accommodating the extra electron density of the incoming nucleophile. The π-deficient pyridine **5a**, on the other hand, would have little difficulty in delocalizing the excess negative charge. The ease of charge delocalization and consequent stability of the crucial seven-membered-ring fused intermediates is also reflected in the differential ability of the five- and six-membered-ring heterocycles to undergo translocative rearrangements. Thus, while **5a** yielded **8** exclusively, the conversion **1** → **3** (≤50%) was always accompanied by the production of an equimolar amount of the corresponding vinylogous amino–nitrile imidazole or pyrazole.[1]

Scheme VII



15 **16** **17**

Finally, we extended the above rearrangement to the π-neutral benzene systems. The imidate **15** (Scheme VII) was analogously prepared from anthranilonitrile and reacted with excess methylhydrazine at room temperature. The product 4-(β-methylhydrazino)quinazoline (**16**), obtained in 86% yield, was thermolyzed in toluene–methanol–TFA to provide the translocated product, 1-methyl-3-(2-aminophenyl)-1,2,4-triazole (**17**), in 96% yield. The reactions are presumed to proceed mechanistically in a similar manner as described for the pyridine system.

In summary, we have demonstrated the versatility of the "translocative" rearrangement which we recently reported.[1] During the course of this endeavor, we have also discovered

two important synthetic transformations: First, fusion of a 4-(β-methylhydrazino)pyrimidine nucleus onto a heterocycle (e.g., **6**) or a carbocycle (e.g., **16**). The method is unique in that the other conceivable procedures can only yield fused 4-(α-substituted hydrazino)pyrimidines, e.g., reaction of 6-chloropurine with methylhydrazine to give 6-(α-methylhydrazino)purine.[11] Second, the above pyrido- or benzo-fused pyrimidines have been converted into the corresponding pyrido- or phenyl-substituted 1,2,4-triazole derivatives. The latter compounds are the isosteric analogues of the biologically and medicinally important natural products, nicotyrines.[12] The syntheses of these analogues would otherwise be difficult by conventional methods. Furthermore, we have discovered that each of the above transformations involves a novel rearrangement. The two rearrangements, taken together, amount to the translocation of an (*N*-amino-*N*-methylamino)methylene [$NH_2N(Me)CH$=] group from a heterocyclic or carbocyclic hydrazidine side chain (e.g., **5a**) to the vinylogous nitrile function to form a triazole ring (e.g., **8**). The rearrangements may carry further scope for synthetic utility and mechanistic investigations.

Experimental Section

Nuclear magnetic resonance spectra were recorded on an IBM NR/80 80-MHz or a GE-GN 500-MHz spectrometer. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet) integration. For ^{15}N NMR, nitromethane was employed as an external reference standard and the chemical shifts are expressed after conversion to the liquid NH_3 scale, $\delta = 0$. Electron-impact (EI) and chemical-ionization (CI) mass spectra were performed at the School of Pharmacy, University of Maryland at Baltimore, on a Du Pont 21-490 mass spectrometer with a 21-094 data system and an Extranuclear Simulscan GC/MS instrument. Infrared spectra were obtained on a Perkin-Elmer 1420 ratio recording instrument. Elemental microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Melting points were detemined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{15}N-enriched (17.2%) ammonia gas was purchased from Merck & Co., Inc., St. Louis, MO.

Methyl *N*-(3-Cyanopyridin-2-yl)methanimidate (4). A mixture of 2-aminonicotinonitrile (600 mg, 5 mmol), trimethyl orthoformate (20 mL), and trifluoroacetic acid (0.025 mL, 0.32 mmol) was heated at reflux under N_2 for 1 h. The reaction mixture was cooled and evaporated to dryness on a rotary evaporator under anhydrous conditions. The residual solvent was removed on a Kügelrohr apparatus [25 °C (0.7 mmHg)] to obtain a moisture-sensitive solid, which was directly employed in the next stage without further purification: ^1H NMR (Me_2SO-d_6) δ 3.95 (s, 3, OMe), 7.35 (dd, J = 4.9 and 7.8 Hz, 1, pyr-H), 8.26 (dd, J = 7.8 and 1.9 Hz, 1, pyr-H), 8.59 (dd, J = 4.9 and 1.9 Hz, 1, pyr-H), 8.61 (s, 1, imidate CH).

***cis*- and *trans*-*N*-Amino-*N*-methyl-*N'*-(3-cyanopyridin-2-yl)formamidine (5a).** To a well-stirring solution of 98% methylhydrazine (0.25 mL, 4.7 mmol) in dry acetonitrile (10 mL), cooled in an ice–water bath, was added the entire quantity of the reagent **4**, prepared above. The reaction mixture was stirred at 0 °C, under N_2, for 15 min. The solvent was removed on a Kügelrohr apparatus [25 °C (0.7 mmHg)] to obtain **5a** (530 mg, 3.03 mmol), 61%): ^1H NMR (Me_2SO-d_6) δ 3.27 (s, 3, Me), 3.29 (s, 3, Me), 5.33 (s, 2, NH_2, exchangeable with D_2O), 5.55 (s, 2, NH_2, exchangeable with D_2O), 6.94 (dd, J = 5.0 and 7.7 Hz, 1, pyr-H), 7.0 (dd, J = 5.0 and 7.7 Hz, 1, pyr-H), 8.0 (dd, J = 7.7 and 1.9 Hz, 1, pyr-H), 8.0 (dd, J = 7.7 and 1.9 Hz, 1, pyr-H), 8.37 (dd, J = 5.0 and 1.9 Hz, 1, pyr-H), 8.37 (dd, J = 5.0 and 1.9 Hz, 1, pyr-H), 8.65 (s, 1, hydrazidine CH), 8.71 (s, 1, hydrazidine CH); IR (KBr) 2220 (C≡N) cm^{-1}.

An attempted separation of cis and trans isomers of **5a** by flash chromatography on a silica gel column resulted in the quantitative isolation of **6** (see below).

4-(β-Methylhydrazino)pyrido[2,3-*d*]pyrimidine (6). Method A. Reaction of 4 with Methylhydrazine. The procedure employed here is the same as the one described for **5a** above except that (a) 0.3 mL (5.64 mmol) of methylhydrazine was employed and (b) after the addition of the reagent **4**, the reaction mixture was stirred at room temperature overnight. Compound **6** was obtained as a solid, which was recrystallized from acetonitrile as bright yellow needles (400 mg, 2.29 mmol, 46%): mp 156–158 °C; ^1H NMR (Me_2SO-d_6) δ 2.80 (s, 3, Me), 7.26 (dd, J = 8.0 and 4.7 Hz, 1, pyr-H), 7.92 (s, 1, triazepine CH), 8.15 (d, J = 8.0 Hz, 1, pyr-H), 8.43 (d, J = 4.7 Hz, 1, pyr-H); mass spectrum (70 eV), m/e 175 (M^+), 146 ($M^+ - NCH_3$, 100); UV λ_{max} (EtOH) 345 nm (ε 6550).

Anal. Calcd for $C_8H_9N_5$: C, 54.84; H, 5.18; N, 39.98. Found: C, 54.78; H, 5.19; N, 39.93.

Method B. Reaction of 5a with Methylhydrazine. A mixture of **5a** (250 mg, 1.43 mmol), methylhydrazine (0.1 mL, 1.88 mmol), and dry acetonitrile (10 mL) was stirred at room temperature overnight. The solvent was evaporated to dryness, and the residue was recrystallized from acetonitrile as bright yellow needles of **6** (220 mg, 1.26 mmol, 88%), mp 156–158 °C. The ^1H NMR and mass spectral data of this compound were identical with those of **6** obtained by method A.

Method C. Purification of 5a by Flash Chromatography. A solution of **5a** (265 mg, 1.5 mmol) in acetonitrile (10 mL) was mixed with 1 g of silica gel (40–63 μm), and the mixture was evaporated to dryness on a rotary evaporator. The residue was suspended in 10 mL of $CHCl_3$, and the resulting slurry was loaded onto a flash chromatography column packed with silica gel (40–63 μm, 15 g) in $CHCl_3$. The column was eluted with a mixture of $CHCl_3$–MeOH (19:1) at 10 mL/min at 4 psi. The appropriate UV-absorbing fractions were pooled and evaporated to obtain **6** as a bright yellow solid (240 mg, 1.37 mmol, 91%). The melting point and ^1H NMR data of this compound were identical with those of **6** prepared by method A or B above.

Method D. Reaction of 5a with H_2O or MeOH. A mixture of **5a** (25 mg, 0.14 mmol), acetonitrile (10 mL), and water (1 mL) or methanol (3 mL) was stirred at room temperature for 48 h. A TLC of the reaction mixture indicated that most of **5a** was converted into **6**. A separate reaction of the same mixture with 0.01 mL of CF_3CO_2H afforded the complete conversion of **5a** into **6** in less than 2 h.

***p*-Nitrobenzaldehyde [[(3-Cyanopyridin-2-yl)imino]-methyl]methylhydrazone (7).** A mixture of **5a** (100 mg, 0.57 mmol), dry acetonitrile (10 mL), and *p*-nitrobenzaldehyde (87 mg, 0.57 mmol) was heated at reflux under N_2 for 30 min. The reaction mixture was cooled and rotary evaporated to dryness. The residue was recrystallized from acetonitrile into yellow crystals of **7** (92 mg, 0.30 mmol, 52%): mp 232–234 °C; ^1H NMR (Me_2SO-d_6) δ 3.64 (s, 3, CH_3), 7.22 (dd, J = 4.8 and 7.7 Hz, 1, pyr-H), 8.0 (d, J = 9.0 Hz, 2, PhH), 8.19 (dd, J = 7.7 and 1.9 Hz, 1, pyr-H), 8.25 (s, 1, hydrazone CH), 8.30 (d, J = 9.0 Hz, 2, PhH), 8.56 (dd, J = 4.8 and 1.9 Hz, 1, pyr-H), 9.23 (s, 1, hydrazidine CH); IR (KBr) 2220 (C≡N) cm^{-1}.

Anal. Calcd for $C_{15}H_{12}N_6O_2$: C, 58.43; H, 3.92; N, 27.26. Found: C, 58.50; H, 3.93; N, 27.16.

2-Amino-3-(1-methyl-1,2,4-triazol-3-yl)pyridine (8). Method A. From 5a. A mixture of **5a** (150 mg, 0.86 mmol), dry toluene (10 mL), dry MeOH (10 mL), and TFA (0.01 mL, 0.13 mmol) was stirred at room temperature for 30 h. The reaction mixture was mixed with silica gel (40–63 μm, 2 g) and rotary evaporated to dryness. The residue was suspended in 10 mL of $CHCl_3$, and the resulting slurry was loaded onto a flash chromatography column packed with silica gel (40–63 μm, 20 g) in $CHCl_3$. The column was eluted with a mixture of $CHCl_3$–MeOH (19:1) at 10 mL/min at 5 psi. The appropriate UV-absorbing fractions were pooled and evaporated to obtain a solid, which was recrystallized from benzene into colorless crystals of **8** (125 mg, 0.71 mmol, 83%): mp 142–143 °C; ^1H NMR (Me_2SO-d_6) δ 3.95 (s, 3, Me), 6.65 (dd, J = 4.8 and 7.6 Hz, 1, pyr-H), 6.98 (br s, 2, NH_2, exchangeable with D_2O), 8.03 (dd, J = 1.9 and 4.8 Hz, 1, pyr-H), 8.20 (dd, J = 1.9 and 7.6 Hz, 1, pyr-H), 8.58 (s, 1, triazole CH).

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Anal. Calcd for $C_8H_9N_5$: C, 54.84; H, 5.18; N, 39.98. Found: C, 54.77; H, 5.22; N, 39.91.

A monotrifluoroacetic acid salt of **8**, prepared for X-ray crystallography, exhibited the following data: colorless crystals from acetonitrile; 96%; mp 162–164 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.99 (s, 3, CH_3), 7.0 (dd, J = 7.6 and 6.0 Hz, 1, pyr-H), 8.13 (dd, J = 6.0 and 1.8 Hz, 1, pyr-*H*) 8.61 (dd, J = 7.6 and 1.8 Hz, 1, pyr-H), 8.74 (s, 1, triazole CH); mass spectrum (70 eV), m/e 175 ($M^+ - CF_3CO_2H$), 159 ($M^+ - CF_3CO_2H - NH_2$), 148 ($M^+ - CF_3CO_2H - HCN$); UV λ_{max} (EtOH) 324 (ϵ 4700), 254 nm (3000), (pH 0.3) 328 (5400), 254 (3800).

Anal. Calcd for $C_{10}H_{10}F_3N_5O_2$: C, 41.53; H, 3.49; N, 24.22. Found: C, 41.57; H, 3.49; N, 24.25.

Method B. From 6. A mixture of **6** (150 mg, 0.86 mmol), dry toluene (10 mL), dry MeOH (10 mL), and TFA (6 μL, 0.08 mmol) was heated at reflux, under N_2, for 6 h. The rest of the procedure is the same as described above in method A. The melting point, ^{1}H NMR, and mass spectral data of the product were identical with those of **8** obtained by method A.

2-([^{15}N]Amino)nicotinonitrile (10). Aboslute EtOH (60 mL) was saturated with anhydrous [^{15}N]ammonia (17.2% enriched) while cooling in an ice–water bath. The solution was then transferred to a stainless steel bomb containing 2-chloronicotinonitrile (2 g, 14.4 mmol). The bomb was sealed and heated in an oil bath at 178 °C for 36 h. The bomb was cooled, and the contents were rotary evaporated to dryness. The residue was triturated with a minimum amount of water and filtered in vacuo. The solid was dissolved in MeOH and mixed with silica gel (40–63 μm, 5 g) and the mixture evaporated to dryness. The residue was suspended in $CHCl_3$ (15 mL), and the resulting slurry was loaded onto a flash chromatography column, packed with a slurry of silica gel (40–63 μm, 60 g) in $CHCl_3$. The column was eluted with a mixture of $CHCl_3$–MeOH (39:1). The appropriate UV-absorbing fractions were pooled and rotary evaporated to obtain colorless crystals of **10** (1.4 g, 11.67 mmol, 81%): mp 131–132 °C (lit.[3] mp 131–133 °C); ^{1}H NMR (Me_2SO-d_6) δ 6.28, 7.39 (d, $J_{^{15}NH}$ = 88.6 Hz, 0.35 H, $^{15}NH_2$, exchangeable with D_2O), 6.63 (dd, J = 4.8 and 7.6 Hz, 1, pyr-H), 6.83 (br, 1.65 H, NH_2, exchangeable with D_2O), 7.85 (dd, J = 1.9 and 7.7 Hz, 1, pyr-H), 8.20 (dd, J = 1.9 and 4.9 Hz, 1, pyr-H); ^{15}N NMR (Me_2SO-d_6) δ 80.8 (t, $J_{^{15}NH}$ = 89.0 Hz, $^{15}NH_2$, exchangeable with D_2O).

2-([^{15}N]Amino)-3-(1-methyl-1,2,4-triazol-3-yl)pyridine (12). Compound **12** was prepared from **10** by employing the procedures described above for **8** from 2-aminonicotinonitrile in the reaction sequence **4** → **5a** → **8**: mp 142–143 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.96 (s, 3, CH_3), 6.47, 7.57 (d, $J_{^{15}NH}$ = 88.0 Hz, 0.34 H, $^{15}NH_2$, exchangeable with D_2O), 6.65 (dd, J = 4.9 and 7.6 Hz, 1, pyr-H), 7.0 (br, 1.66 H, NH_2, exchangeable with D_2O, 8.04 (dd, J = 1.9 and 4.9 Hz, 1, pyr-H), 8.21 (dd, J = 1.9 and 7.6 Hz, 1, pyr-H), 8.59 (s, 1, triazole CH); ^{15}N NMR (Me_2SO-d_6) δ 76.5 (t, $J_{^{15}NH}$ = 88.0 Hz, $^{15}NH_2$, exchangeable with D_2O).

General Procedure for the Conversion 1 → 14. To a solution of compound **1a** or **1b** (1.96 mmol) in a mixture of dry toluene (15 mL) and dry MeOH (5 mL) was added methylhydrazine (0.5 mL, 9.4 mmol), followed by trifluoroacetic acid (0.01 mL, 0.13 mmol). The reaction mixture was heated at reflux under N_2 for 15 h, cooled, and rotary evaporated to dryness. The residue was dissolved in MeOH (20 mL), and the solution was mixed with silica gel (40–63 μm, 2 g). The mixture was evaporated to dryness, and the residue was suspended in 10 mL of $CHCl_3$. The resulting slurry was loaded onto a flash chromatography column, packed with a slurry of silica gel (40–63 μm, 20 g) in $CHCl_3$. The column was eluted with a mixture of $CHCl_3$–MeOH (39:1). The appropriate UV-absorbing fractions were pooled and rotary evaporated to obtain a solid. The percentage yields, melting points, recrystallization solvents, and spectral and analytical data for compounds **14a** and **14b** are given below.

9-Benzyl-6-(β-methylhydrazino)purine (14a): colorless crystals from acetonitrile; 80%; mp 119–120 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.62 (s, 3, CH_3), 5.22 (br, 1, NH, exchangeable with D_2O), 5.41 (s, 2, CH_2), 7.32 (s, 5, Ph), 8.27 (s, 1, CH), 8.30 (s, 1, CH), 9.30 (br, 1, NH, exchangeable with D_2O); mass spectrum (70 eV), m/e 254 (M^+), 225 (M^+ – NMe), 163 ($M^+ - CH_2Ph$); UV λ_{max} (EtOH) 269 nm.

Anal. Calcd for $C_{13}H_{14}N_6$: C, 61.40; H, 5.55; N, 33.05. Found: C, 61.43; H, 5.56; N, 32.96.

1-Methyl-4-(β-methylhydrazino)pyrazolo[3,4-*d*]pyrimidine (14b): colorless crystals from acetonitrile, 58%; mp 205–207 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.58 (s, 3, CH_3), 3.88 (s, 3, CH_3), 5.2 (br, 1, NH, exchangeable with D_2O), 8.13 (s, 1, CH), 8.14 (s, 1, CH), 9.2 (br, 1, NH exchangeable with D_2O); mass spectrum (70 eV), m/e 178 (M^+), 163 ($M^+ - CH_3$), 149 ($M^+ - NCH_3$); UV λ_{max} (EtOH) 281 nm (ϵ 10000), (pH 0.2) 264 (16300).

Anal. Calcd for $C_7H_{10}N_6$: C, 47.18; H, 5.66; N, 47.16. Found: C, 47.08; H, 5.67; N, 47.04.

Attempted Rearrangement of 14 to 3. A mixture of **14a** or **14b** (2.13 mmol), dry toluene (15 mL), dry MeOH (15 mL), and trifluoroacetic acid (0.05 mL, 0.65 mmol) was heated at reflux under N_2 for up to 7 days. A TLC of the reaction mixture in three different solvent systems, taken at different time intervals, indicated no change. The reaction mixture was cooled and rotary evaporated to dryness to recover the starting material.

Methyl *N*-(2-Cyanophenyl)methanimidate (15). A mixture of anthranilonitrile (2 g, 17 mmol), trimethyl orthoformate (50 mL), and trifluoroacetic acid (0.05 mL, 0.65 mmol) was heated at reflux under N_2 for 1 h. The reaction mixture was cooled and rotary evaporated to obtain a thick oil, which was distilled in a Kügelrohr apparatus [oven temperature 85–95 °C (0.4 mmHg)] to obtain **15** as a colorless liquid, which was directly employed in the next step (2.35 g, 85%): ^{1}H NMR (Me_2SO-d_6) δ 3.91 (s, 3, OCH_3), 7.16–7.34 (m, 2, Ph), 7.53–7.78 (m, 2, Ph), 8.13 (s, 1, imidate CH); IR (neat) 2220 cm^{-1}.

4-(β-Methylhydrazino)quinazoline (16). To a well-stirring solution of 98% methylhydrazine (0.76 mL, 14.6 mmol) in methylene chloride (20 mL), cooled in an ice–water bath, was added dropwise a solution of the imidate **15** (2.35 g, 14.6 mmol) during a period of 10 min. The reaction mixture as stirred overnight. The pale yellow solid formed was collected by filtration, dried, and recrystallized from acetonitrile into pale yellow flakes of **16** (2.2 g, 12.64 mmol, 87%): mp 157–159 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.70 (s, 3, CH_3), 7.26–7.74 (m, 3, Ph*H*), 8.03 (d, J = 7.8 Hz, 1, Ph*H*), 8.22 (s, 1, triazepine CH); mass spectrum (70 eV), m/e 174 (M^+), 159 ($M^+ - CH_3$), 145 ($M^+ - NCH_3$, 100); UV λ_{max} (EtOH) 322 (ϵ 6830), 315 (7250), 234 nm (8360), (pH 0.2) 310 (8640), 245 (1180), (pH 13) 350 (8570), 270 (6200).

Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.16. Found: C, 61.80; H, 5.83; N, 32.04.

1-Methyl-3-(2-aminophenyl)-1,2,4-triazole (17). A mixture of **16** (500 mg, 2.87 mmol), dry MeOH (20 mL), dry toluene (10 mL), and trifluoroacetic acid (0.05 mL, 0.64 mmol) was heated at reflux under N_2 for 7 h. The reaction mixture was cooled and rotary evaporated to dryness. The residue was extracted with acetonitrile (3 × 50 mL), the combined extracts were treated with decoloring charcoal and filtered, and the filtrate was evaporated to dryness. The solid residue was recrystallized from a minimum amount of acetonitrile into colorless crystals of **17** (450 mg, 2.59 mmol, 90%): mp 145–148 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.92 (s, 1, CH_3), 6.33 (br s, 2, NH_2, exchangeable with D_2O), 6.49–7.18 (m, 3, Ph*H*), 7.9 (dd, J = 7.9 and 1.7 Hz, 1, Ph*H*), 8.5 (s, 1, triazole CH); mass spectrum (70 eV), m/e 174 (M^+), 146, 132, 118; UV λ_{max} (EtOH) 318 (ϵ 5500), 248 nm (10400), (pH 13) 316 (5700), 247 (12000).

Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.16. Found: C, 61.98; H, 5.81; N, 32.12.

Single-Crystal X-ray Structure Analyses of 6, 8·TFA, and 14b. Suitable crystals were grown through slow crystallization from appropriate solvents: **6**, pale yellow, from toluene–ligroin; **8**·TFA, colorless, from acetonitrile; **14b**, colorless, from 95% EtOH. Data were collected on a Syntex $P2_1$ four-circle diffractometer at room temperature using graphite monochromated Mo Kα (λ = 0.71069 Å) radiation. The unit cell dimensions were obtained by a least-squares fit of 15 centered reflections in the range of $10° < 2\theta < 25°$. Intensity data were collected by using a $\theta/2\theta$ scan type in the range of $3° < 2\theta < 45°$. Three standard reflections monitored after every 100 reflections did not show any significant change in intensity during data collection. Intensities were corrected for Lorentz and polarization effects. The structure was solved and all non-hydrogen atoms were found by using results of SHELXS86.[13] After several cycles of refinements using SHELX76,[14]

(13) Sheldrick, G. M. "SHELXS86," Program for Crystal Structure Solution; University of Gottingen, Gottingen, 1986.

the positions of hydrogen atoms were located on a difference Fourier map, except for methyl hydrogens, which were calculated. Hydrogen atoms were included in the refinement with isotropic thermal parameters. Refinement proceeded to convergence by minimizing the function $\sum w(|F_o| - |F_c|)^2$, where the weight, w, is $\sigma(F)^{-2}$. The discrepancy indices $R = \sum||F_o| - |F_c||/\sum|F_o|$ and $R_w = |\sum w(|F_o| - |F_c|)^2/\sum w(|F_o|)|^{1/2}$ are presented below.

Crystallographic Data. A. Compound 6: $C_8H_9N_5$, space group $C2/c$, a = 23.32 (12) Å, b = 3.870 (2) Å, c = 18.235 (9) Å, β = 91.68 (2)°, V = 1645.3 (9) Å^3, Z = 8, D_{calcd} = 1.41 g cm^{-3}, μ (Mo Kα) = 0.09 mm^{-1}. Number of unique reflections = 1082, reflections with $1 \geq 3\sigma(1)$ = 783; R = 0.054, R_w = 0.059.

B. Compound 8·CF$_3$CO$_2$H: $C_{10}H_{10}N_5O_2F_3$, space group $P2_1/n$, a = 4.615 (2) Å, b = 26.328 (9) Å, c = 10.224 (5) Å, β = 90.59 (4)°, V = 1242 (1) Å^3, Z = 4, D_{calcd} = 1.55 g cm^{-3}, μ (Mo Kα) = 0.13 mm^{-1}. Number of unique reflections = 1611, reflections with $1 \geq 3\sigma(1)$ = 1192; R = 0.054, R_w = 0.060.

C. Compound 14b: $C_7H_{10}N_6$, space group $P2_1/c$, a = 7.495 (5) Å, b = 16.456 (9) Å, c = 7.427 (3) Å, β = 108.85 (4)°, V = 866.9 (8) Å^3, Z = 4, D_{calcd} = 1.37 g cm^{-3}, μ (Mo Kα) = 0.58 cm^{-1}. Number of unique reflections = 1129, reflections with $1 \geq 3\sigma(1)$ = 962; R = 0.046, R_w = 0.062.

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Supplementary Material Available: Tables of bond lengths, bond angles, torsional angles, and positional parameters for compounds **6**, **8**·TFA, and **14b** (9 pages). Ordering information is given on any current masthead page.

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Synthesis of Amino-Substituted Dodecahedranes, Secododecahedranes, and Homododecahedranes and Their Antiviral Relationship to 1-Aminoadamantane

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Several spherically shaped molecules carrying an amino head group have been prepared and assayed for antiviral activity against influenza A virus. The secododecahedrane derivatives **4** and **5** have been arrived at through suitable chemical manipulation of intermediates utilized in the synthesis of dodecahedrane itself. The important relay precursor to dodecahedranes **6** and **7** is amide **16**, available by reaction of ester **15** with dimethylaluminum amide. Dehydration to nitrile **19** and subsequent catalytic hydrogenation gave **6**. In order to bypass complications often brought on by the steric bulk of the dodecahedrane framework and insolubility factors, Hoffmann rearrangement of **16** was effected with the highly reactive [bis(trifluoroacetoxy)iodo]benzene reagent. Treatment of bromododecahedrane **12** with trimethylsilyl azide and stannic chloride gave rise to the azahomododecahedrane derivative **22**, the immediate precursor of **23**. Finally, the results of the bioassays are presented.

There has been considerable recent interest in the synthesis of dodecahedrane (**1**),[1-3] the structurally most complex and aesthetically appealing member of the C_nH_n convex polyhedra (n = 20). Derivatives of **1**, although necessarily of symmetry lower than the unrivaled I_h level of the parent hydrocarbon, hold high interest in their own right. Knowledge of the magnitude of structural distortion incurred by replacing methine hydrogen by larger substituents of divergent electronic character is one aspect that has received some attention.[4-7] During the course of our successful efforts to prepare **1**,[8] it proved feasible to incorporate pendant alkyl groups early in the scheme and to access by this means the monomethyl derivative,[9] several dimethyl isomers,[10,11] and the 1,4,16-trimethyl-substituted hydrocarbon.[11] For the purpose of introducing a greater array of functional groups, recourse has since been made to engaging dodecahedrane itself directly into chemical reaction.[12] More recently, controlled 1,16-disubstitution of **1** has also become possible via its D_{3d} symmetric dication **2**,[13] and direct annulation of a cyclopropane ring to the sphere as in **3** has been realized.[14,15]

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