197–198.5 °C; ^{1}H NMR (see Table I). Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.62; H, 4.89; N, 4.01. Found: C, 72.28; H, 5.01; N, 3.83.

***trans*-1,2-Dihydroxy-1,2-dihydrobenz[*c*]acridine (30).** Hydrolysis of dihydrodiol diacetate **29** (140 mg) in dry THF (6 mL) and anhydrous MeOH (250 mL) with ammonia gas was effected as described for the preparation of **20**, except that the reaction time was 20 h. Workup as described previously gave brownish crystalline solid **30**: 70 mg (64%); mp 160–162 °C; ^{1}H NMR (see Table I).

Benz[*c*]acridine 5,6-Oxide (31). Benz[*c*]acridine (100 mg) was dissolved in 15 mL $CHCl_3$ and added to a solution of 12 mL of Chlorox buffered to pH 8.5 with 0.8 M sodium phosphate containing tetrabutylammonium hydrogen phosphate (74 mg). The biphasic solution was stirred in a glass-stoppered flask at room temperature for 5 h. The mixture was diluted with 60 mL of ether. The usual workup gave a colorless crystalline solid from which **31** was obtained after two recrystallizations from ether as colorless needles: mp 153–154 °C; yield 45 mg (42%); NMR (60 MHz, $CDCl_3$) δ 4.47, 4.60 ($H_{5,6}$, $J_{5,6}$ = 4.2 Hz), 7.26–8.33 (m, 8 H), 8.25 (s, H_7), 8.80–9.13 (m, H_1).

***trans*-5,6-Dihydroxy-5,6-dihydrobenz[*c*]acridine.** A solution of the above epoxide (300 mg) was dissolved in 50 mL dioxane and 10 mL 25% aqueous AcOH. The solution was stirred at 35 °C under N_2 for 48 h. Most of the dioxane was removed, and the residue was stirred with 10% ice-cold NaOH (20 mL) and extracted with EtOAc. The EtOAc layer was washed with water, dried over Na_2SO_4, and distilled to give a residue. It was chromatographed over silica gel, and the most polar major product was eluted with EtOAc to give 75 mg of the colorless solid. It was treated with Ac_2O (10 mL) and pyridine (2 mL) at room temperature for 20 h to give the diacetate, which was recrystallized twice from ethyl acetate–hexane to yield 71 mg of pale yellow needles: mp 157–158 °C; ^{1}H NMR (100 MHz) δ 1.95 (s, 3 H), 1.98 (s, 3 H), 6.16, 6.26 ($H_{5,6}$, J = 4.7 Hz), 7.36–8.32 (m, 8 H), 8.56–8.80 (m, H_1). Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.62; H, 4.89; N, 4.01. Found: C, 72.76; H, 4.83; N, 3.88.

The hydrolysis of this diacetate was effected in 50 mL of methanol saturated with NH_3 gas at room temperature for 6 h. Most of the methanol was removed, and the residue was diluted with water. The colorless solid so separated was centrifuged and triturated with 3% EtOAc–hexane to give 42 mg of *trans*-diol: mp 182–184 °C; ^{1}H NMR (100 MHz, CD_3COCD_3 + CD_3OD) δ 4.86 (br s, 2 H), 7.40–8.22 (m, 7 H), 8.40–8.64 (m, 2 H).

(±)-3α,4β-Dihydroxy-1α,2α-epoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (32). A mixture of 3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine (50 mg) and *m*-CPBA (250 mg) in anhydrous THF (25 mL) was stirred at room temperature under N_2 for 1 h. The mixture was diluted with ether, extracted with ice-cold 2% NaOH and water, dried (Na_2SO_4), and concentrated to give diol epoxide **32** (38 mg, 72%) as a pale yellow solid: mp 198–200 °C dec; ^{1}H NMR (100 MHz, Me_2SO-d_6) 3.72–4.0 (m, H_2, H_3), 4.40–4.68 (m, H_4), 5.56 (d, H_1), 5.64 (d, OH_3), 5.86 (d, OH_4), 7.5–8.4 (m, 6 H), 9.15 (s, H_7); $J_{1,2}$ = 4.0 Hz, $J_{3,4}$ = 8.4 Hz, $J_{4,OH}$ = 6.5 Hz, $J_{3,OH}$ = 6.6 Hz.

(±)-3α,4β-Dihydroxy-1β,2β-epoxy-1,2,3,4-tetrahydrobenz[*c*]acridine (33). To a stirred solution of dihydrodiol **27** (26 mg) in THF (8 mL) at 0 °C under argon was added H_2O (2 mL), *N*-bromoacetamide (16 mg), and 1 drop of concentrated HCl. The solution was stirred for 1 h at 0–5 °C. EtOAc was added, and the reaction was worked up in the usual manner to give a solid, which was triturated with ether to give the bromo triol (±)-2α-bromo-1β,3α,4β-trihydroxy-1,2,3,4-tetrahydrobenz[*c*]acridine as a colorless, crystalline solid: 32 mg (90%); mp 142–144 °C dec; NMR (Me_2SO-d_6, CD_3OD) δ 4.26 (dd, H_3), 4.6–4.8 (m, H_2, H_4), 6.08 (d, H_1), 7.42–8.78 (m, 6 H), 9.04 (s, H_7); $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 2.2 Hz, $J_{3,4}$ = 7.0 Hz.

To a stirred solution of the bromotriol (45 mg) in anhydrous THF (20 mL) was added KO-*t*-Bu (75 mg), and the mixture was stirred under Ar for 14 min at room temperature. EtOAc was added, and the organic phase was extracted twice with cold water. The usual workup gave a solid which was triturated with petroleum ether to give diol epoxide **33**: 23 mg (66%); mp 190–191 °C dec; NMR (Me_2SO-d_6, CD_3OD) 3.89 (m, H_2), 4.16 (m, H_3), 4.67 (d, H_4), 5.33 (d, H_1), 7.52–8.32 (m, 6 H), 8.12 (s, H_7); $J_{3,4} \approx 2.5$ Hz, $J_{1,2}$ = 4.0 Hz.

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Registry No. 1, 225-51-4; 3, 19730-91-7; 4, 54538-09-9; 5, 78167-75-6; (±)-6, 78167-76-7; 7, 78167-77-8; 8, 78186-15-9; 9, 78167-78-9; (±)-10, 78167-79-0; 11, 78167-80-3; 12, 77305-66-9; 13, 78167-81-4; (±)-14, 78167-82-5; (±)-15, 78167-83-6; (±)-16, 78167-84-7; (±)-17 (isomer 1), 78167-85-8; (±)-17 (isomer 2), 78215-27-7; (±)-18, 78167-86-9; (±)-19, 78167-87-0; (±)-20, 78167-88-1; (±)-21, 78167-89-2; (±)-22, 78167-90-5; (±)-23, 78167-91-6; 24, 78215-28-8; (±)-25, 78167-92-7; (±)-26, 78167-93-8; (±)-27, 78167-94-9; 28, 78167-95-0; (±)-29, 78167-96-1; (±)-30, 78167-97-2; (±)-31, 78167-98-3; (±)-32, 78167-99-4; (±)-33, 78215-29-9; (±)-11-hydroxy-8,9,10,11-tetrahydrobenz[*c*]acridine, 78168-00-0; (±)-10,11-epoxy-8,9,10,11-tetrahydrobenz[*c*]acridine, 78168-01-1; (±)-*trans*-10,11-dihydroxy-8,9,10,11-tetrahydrobenz[*c*]acridine, 78168-02-2; 1,2,3,4,7,12-hexahydrobenz[*c*]acridine, 78168-03-3; (±)-4-acetoxy-1,2,3,4-tetrahydrobenz[*c*]acridine, 78168-04-4; (±)-*trans*-2-bromo-1-hydroxy-1,2,3,4-tetrahydrobenz[*c*]acridine, 78168-05-5; (±)-*trans*-5,6-dihydroxy-5,6-dihydrobenz[*c*]acridine, 78186-09-1; (±)-*trans*-5,6-diacetoxy-5,6-dihydrobenz[*c*]acridine, 78168-06-6; (±)-2α-bromo-1β,3α,4β-trihydroxy-1,2,3,4-tetrahydrobenz[*c*]acridine, 78168-07-7.

Guanine Analogues. Allyl-Substituted Aminoimidazo[1,5-*a*]-1,3,5-triazinones Formed by Cyclization–Rearrangement

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Syntheses of allylimidazo[1,5-*a*]-1,3,5-triazinones, which are analogues of N(9)-substituted guanines, have been accomplished by cyclization–rearrangement. Condensation of ethyl 2-cyano-2-formamido-4-pentenoate and ethyl 2-acetamido-2-cyano-4-pentenoate with guanidine yielded substituted 5-allyl-4,5-dihydropyrimidin-4-ones. Treatment of these 5-allyl-4,5-dihydropyrimidin-4-ones with chlorotrimethylsilane and hexamethyldisilazane in pyridine gave the correspondingly substituted allylimidazo[1,5-*a*]-1,3,5-triazinones by a rearrangement that appears to proceed through 5-allylguanines as transient intermediates. Structures were established in this series on the basis of precursors and routes of synthesis, IR spectra, ^{1}H and ^{13}C NMR spectra, mass spectra, and a final catalytic hydrogenation.

Recently, we reported that treatment of 4,5-dihydropyrimidin-4-ones **1a–e** in pyridine with chlorotrimethylsilane and hexamethyldisilazane[1] leads effectively to the correspondingly substituted imidazo[1,5-*a*]-1,3,5-triazin-

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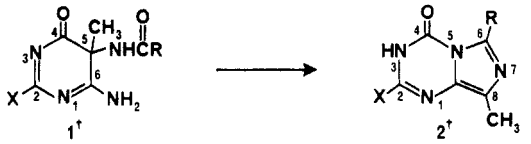
4-ones **2a–e**, analogues of N(9)-substituted guanines and

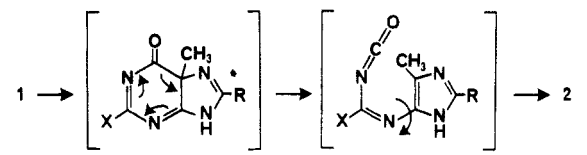


1a, R = H, X = NH_2
b, R = H, X = SH
c, R = CH_3, X = NH_2
d, R = CH_3, X = $N(CH_3)_2$
e, R = CH_3, X = SH

2a, R = H, X = NH_2
b, R = H, X = SH
c, R = CH_3, X = NH_2
d, R = CH_3, X = $N(CH_3)_2$
e, R = CH_3, X = SH
f, R = H, X = H
g, R = CH_3, X = H

† The listings of R and X conveniently indicate substitution but do not necessarily indicate the favored tautomeric form.

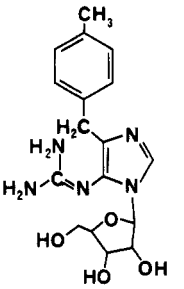
xanthines, and we established thereby the generality of this synthetic approach to imidazo[1,5-*a*]-1,3,5-triazin-4-ones with variation in substitution at C(2) (see numbering system in 1) and in the C(5)-amide group of the 4,5-dihydropyrimidin-4-one precursors.[2,3] Raney nickel desulfurization of compounds **2b** and **2e** in aqueous ammonia gave the imidazo[1,5-*a*]-1,3,5-triazin-4-ones **2f** and **2g**, analogues of N(9)-substituted hypoxanthines. Although the sequence of events for the observed cyclization–rearrangement has not been established, initial cyclization of a trimethylsilylated 1 to add an appended imidazole-type ring would provide better stabilization for C(4)–C(5) cleavage (either heterolytically or electrocyclically) than would be provided before cyclization of the five-membered ring. One possible route of 1 to 2 for stabilization of the system would then result, e.g., from an electrocyclic conversion[4] of 3, a C(5)-substituted purine, to 4 (X is tri-



3 4

methylsilylated in all but **1d**) and rotation about the original N(1)–C(6) bond (see numbering system in 1) to allow closure of the isocyanate grouping onto the original 6 amino group.

Our results indicated that the existence of a C(5)-alkylated guanine would be transient and that an intermediate of this type, if formed, would tend to undergo facile ring cleavage and/or rearrangement. This interpretation is consistent with the recent disclosure that the reaction of *p*-methylbenzyl chloride with guanosine in neutral aqueous solution yields 4-(*p*-methylbenzyl)-5-guanidino-1-β-D-ribofuranosylimidazole (**5**) in addition to N^2-, O^6-, and 7-(*p*-methylbenzyl)guanosine.[5] Direct attack of the



5

very active electrophile (compared with benzyl chloride in aqueous solution) at the C(5) position of the nucleoside would give a C(5)-aralkylated guanosine analogous to **3**. Subsequent fission (electrocyclic or hydrolytic) of the pyrimidine ring followed by decarboxylation would complete the plausible route to compound **5**.[5] The common requirement for the structural changes in both series, 1 → 2 and guanosine → **5**, is a 5-substituted guanine intermediate.

Prior to our observation of the cyclization–rearrangement 1 → 2, it was established in this laboratory that the displacement reaction of 2-amino-6-chloropurine (**6**) with the sodium salts of allylic alcohols proceeds through an O^6-ether (e.g., **7**) to yield a C(8)-substituted guanine (e.g., **8**) as shown in Scheme I.[6–8] The O^6 to C(8) rearrangement, which proceeds with overall allylic retention and with greatest facility through anionic species, occurs intramolecularly in the presence of alkoxide, on the basis of double-labeling experiments.[7] Examination of possible rearrangement mechanisms proceeding via *N*-allylguanines gave negative results,[7–9] which led to the conclusion that the rearrangement involved two anionic [3,3] sigmatropic shifts via a C(5)-substituted purine. By blocking the C(8) position of the purine ring with a methyl group, we sought to trap the C(5) intermediate or to redirect the migrating group.[10] Thereby, another allylic rearrangement was revealed in which the overall migration, with allylic retention, is from O^6 to the N(3) and N(7) positions of the guanine ring (Scheme II). Reaction sequences in which C(5)-allylic C(8)-blocked guanines were proposed in the rearrangement of compound **9** to the guanines **11** and **12**, also in the presence of alkoxide, were based on the unblocked results, on simple product analysis, and on the exclusion of other intramolecular routes.

Comparison of the mechanisms proposed for the cyclization–rearrangement which leads to imidazo[1,5-*a*]-1,3,5-triazine products and for the rearrangements of O^6-allylic guanines to C(8)-allylic guanines and N(3)- plus N(7)-allylic guanines reveals the possibility of generating C(5)-allylic guanine intermediates which could give 8-allylimidazo[1,5-*a*]-1,3,5-triazines and/or allyl-substituted guanines. Replacement of the C(5) methyl of compounds **1a** and **1c** with an allyl group would provide 4,5-dihydropyrimidin-4-ones capable of giving C(5)-allylic guanines on cyclization of the imidazole-type ring. In order to

(1) The treatment of 4,5-dihydropyrimidin-4-ones 1a–e with these reagents for closure to an imidazo ring was based on the work of Vorbrüggen involving the amination of O-trimethylsilylated heterocycles. Vorbrüggen, H.; Krolikiewicz, K.; Niedballa, U. *Justus Liebigs Ann. Chem.* **1975**, 988.

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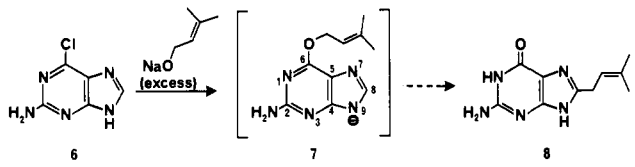
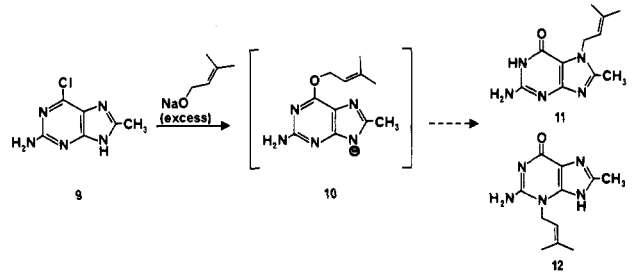
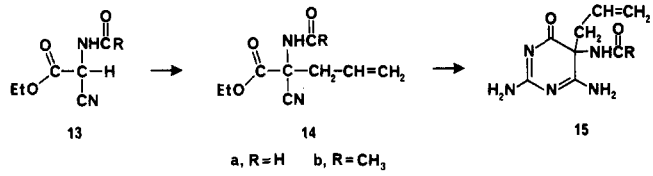
Scheme I



Scheme II



Scheme III



a, R = H b, R = CH_3

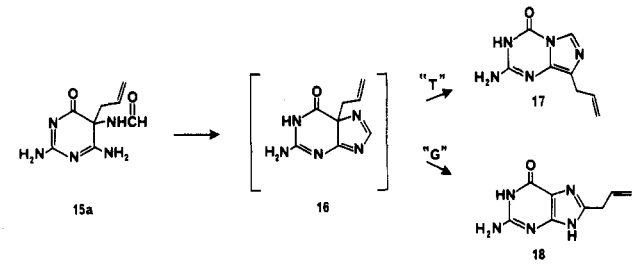
evaluate further the generality of the cyclization–rearrangement leading to imidazo[1,5-a]-1,3,5-triazines, we prepared the 4,5-dihydropyrimidin-4-ones **15a** and **15b** as shown in Scheme III. Dehydrative closure of **15a** to an imidazole-type ring could give the C(5)-allylic guanine **16**, which might then afford 8-allyl-2-aminoimidazo[1,5-a]-1,3,5-triazin-4(3*H*)-one (**17**) and/or, under the requisite conditions, 8-allylguanine (**18**,[7] Scheme IV). Similarly, cyclization of **15b** might lead to 8-allyl-2-amino-6-methylimidazo[1,5-a]-1,3,5-triazin-4(3*H*)-one (**20**) and/or a mixture of *N*(3)- and *N*(7)-allylguanines (**21** and **22**,[10] Scheme V). The conditions under which the sequences have been tested are those which, in our experience, would actually favor imidazo[1,5-a]-1,3,5-triazine products and, if these were obtained, would further establish the generality of the rearrangement approach to the synthesis of such compounds.[11]

Results and Discussion

The condensation of disubstituted cyanoacetic esters with guanidine was shown very early to provide derivatives of 2,6-diamino-4,5-dihydropyrimidin-4-ones.[12] A synthetic route based on this precedent was adapted to the preparation of the 5-methyl-4,5-dihydropyrimidin-4-ones **1a–e**[2,3] and now to the preparation of the 5-allyl-4,5-dihydropyrimidin-4-ones **15a** and **15b** (Scheme III). Treatment of an ethanolic solution of ethyl 2-cyano-2-formamidoacetate (**13a**)[3] with 3-bromo-1-propene in the presence of sodium ethoxide gave ethyl 2-cyano-2-formamido-4-pentenoate (**14a**) in 90% yield.

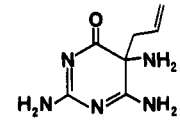
Condensation of ethyl 2-acetamido-2-cyano-4-pentenoate (**14b**)[13] with guanidine in ethanol containing 1 molar equiv of sodium ethoxide, followed by the addition of ammonium iodide to pH 7, yielded the 4,5-dihydropyrimidin-4-one **15b** in 60% yield after crystallization from aqueous ethanol.

Scheme IV[a]



[a] The guanine or "G" route proceeds through the anion of **16** followed by neutralization.

The most efficient conditions found for the condensation of guanidine with **14a** to give the 4,5-dihydro-5-formamidopyrimidin-4-one **15a** differ from those employed in the preparation of **15b**, which afforded a mixture of **15a** and **23**. Instead, treatment of **14a** with guanidine in

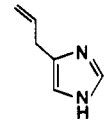


ethanol in the absence of sodium ethoxide resulted in **15a** in 30% yield, free from **23**. The sensitivity of **15a** to hydrolysis made it difficult for us to optimize the yield.

The ^{13}C NMR spectra of compounds **15a,b** and **23** are consistent with the structures as illustrated. For example, **15a** shows four signals between 159 and 178 ppm corresponding to C(2), C(4), C(6), and the formyl carbon, signals at 42.8, 123.9, and 128.1 ppm are due to the allyl group carbons, and the crucial resonance at 59.6 ppm establishes the presence of the tetrasubstituted C(5). Similarly, signals at 60.6 and 60.8 ppm in the ^{13}C NMR spectra of compounds **15b** and **23** clearly demonstrate the presence of a tetrasubstituted carbon in each.

Treatment of compounds **15a** and **15b** in pyridine with 3 molar equiv each of chlorotrimethylsilane and hexamethyldisilazane at reflux under nitrogen provided an efficient procedure for closure to the imidazo ring to give the substituted imidazo[1,5-a]-1,3,5-triazines **17** and **20**, respectively, as major products. The formamido derivative **15a** demonstrated a marked tendency toward this imidazole ring closure and rearrangement, parallel to the behavior of the formamido derivatives **1a** and **1b** and in contrast to the acetamido derivatives **1c–e** and **15b**, which required prolonged heating at reflux to effect complete product formation.

The judgment that dehydrative closure of compounds **15a** and **15b** gives compounds **17** and **20**, respectively, was based on spectroscopic data and analogy. For example, the ^1H NMR spectrum of compound **20** shows a crucial signal for the methylene protons of the allyl group at δ 3.20–3.30, indicative of C substitution. In close comparison, 4(5)-allylimidazole (**24**)[14] exhibits a signal for the



methylene hydrogens of the allyl group at δ 3.39. By contrast, the ^1H NMR spectra of the *N*-allylguanines **21**

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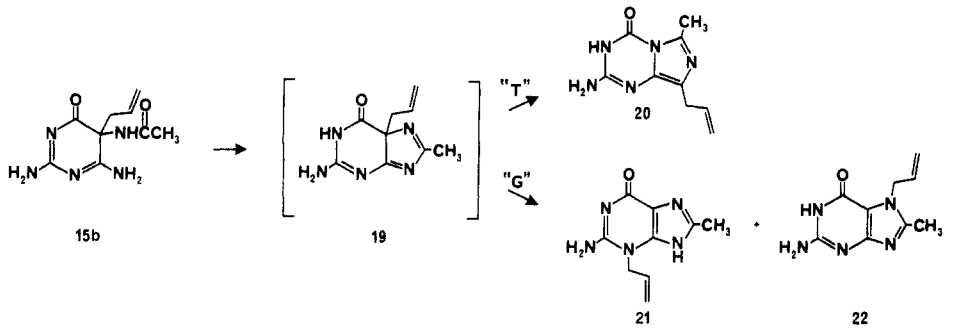
Scheme V[a]



[a] The guanine or "G" route proceeds through the anion of 19 followed by neutralization.

and 22 would be expected to show signals for the methylene hydrogens at lower field than δ 4 (e.g., compounds 11 and 12 exhibit signals at δ 4.82 and 4.62, respectively, for the methylene hydrogens of the isopentenyl side chains). Examination of the ^{1}H NMR spectrum of compound 17 revealed a crucial resonance at 7.90 ppm due to a hydrogen not replaceable with deuterium in D_2O (the C(6) hydrogen) and a signal for the methylene protons centered at 3.20 ppm, indicative of C substitution. A sufficient basis for elimination of 8-allylguanine (18) from consideration as the possible product of the dehydrative rearrangement of 15a was thus provided since 18 does not possess a hydrogen capable of giving rise to the signal observed at 7.90 ppm.

Rearrangement of O^6-allylguanine to 8-allylguanine (18) in the presence of alkoxide had been related by catalytic hydrogenation of 18 to 8-propylguanine, which was identical with an authentic sample of 8-propylguanine prepared by an unequivocal synthesis.[7] That the dehydrative cyclization route from 15a to 16 did not continue on the guanine "G" path but followed the triazinone "T" path under the silylation conditions in pyridine (and in the absence of alkoxide) was observed in the catalytic hydrogenation of 17 to 2-amino-8-propylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (25). Comparison of various spectroscopic and physical properties associated with compounds 25 and 8-propylguanine confirmed their separate identities and thereby established the separate identities of precursor compounds 17 and 18.

Comparison of the IR spectra of the imidazo[1,5-*a*]-1,3,5-triazine 2c and the products of 15a and 15b dehydrative cyclizations provided additional support for assignment of the structures 17 and 20. In addition to possessing a common carbonyl stretching vibration at 1740 cm^{-1}, the IR spectra of each compound in the region between 1700 and 400 cm^{-1} revealed a strikingly similar pattern of absorption bands with maxima centered at about 1540, 1450, 1390, 1340, 1280, and 940 cm^{-1}. Further, the imidazo[1,5-*a*]-1,3,5-triazines 17 and 20 shared absorption maxima centered at about 1000, 760, and 420 cm^{-1}.

The ^{13}C NMR spectra of compounds 17 and 20, which exhibit eight and nine signals, respectively, none of which is indicative of the presence of a tetrasubstituted carbon (i.e., there are no signals to be observed between 70 and 40 ppm), are also consistent with the imidazo[1,5-*a*]-1,3,5-triazine structures as illustrated. Compound 20 shows five signals between 119 and 148 ppm corresponding to C(2), C(4), C(6), C(8), and C(8a), signals at 30.0, 114.7, and 136.9 ppm correspond to the allyl-group carbons, and the signal at 15.9 ppm is due to the *C*(8)-methyl group. The ^{13}C NMR spectrum of compound 17 closely parallels that of the related imidazo[1,5-*a*]triazine 20. Four signals between 121 and 148 ppm are due to the C(2), C(4), C(6), C(8), and C(8a) carbons, and signals at 30.1, 114.9, and 136.8 ppm correspond to the allyl group carbons. As expected on the basis of the ^{1}H NMR spectrum, a crucial signal due to C(6) appears as a doublet in the off-resonance decoupled ^{13}C NMR spectrum of compound 17.[15]

Analysis of the major fragment ions in the mass spectra determined at 10 eV for the 4,5-dihydropyrimidin-4-ones 15a and 15b and the imidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-ones 17 and 20 revealed common features between and within each set of compounds. The mono- and bicyclic heterocycles characteristically showed a predominant molecular ion, with compound 15a being the only exception (relative abundance for M^+ = 27%). The predominant ion for compound 15a was observed at *m/e* 181 (M^+ – CO, 100% relative abundance) and served as an additional indication of the formyl-group lability of this 5-formamidopyrimidin-4-one. Each of the 4,5-dihydropyrimidin-4-one derivatives 15a and 15b fragmented with the neutral loss of HNCO (M^+ – 43). The imidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-ones 17 and 20 showed the loss of the C(6)–N(7) fragment, i.e., HCN and CH_3CN, respectively.

The possibility of successful preparation of imidazo-[1,5-*a*]-1,3,5-triazines with variation in substitution at C(5) of the 4,5-dihydropyrimidin-4-one precursors is of particular interest (a) in view of the analogy between C(8) substitution in the imidazo[1,5-*a*]-1,3,5-triazines 17 and 2f, as examples, and N(9) substitution on guanine and hypoxanthine, respectively, and (b) since substitution at C(5) in the monocyclic heterocycle results in identical substitution on C(8) in the corresponding imidazo[1,5-*a*]-1,3,5-triazine. Incorporation of a ribosyl unit at the C(5) position of appropriate 4,5-dihydropyrimidin-4-ones, if that were possible, would give, on cyclization–rearrangement, imidazo[1,5-*a*]-1,3,5-triazine analogues of naturally occurring nucleosides. In view of the strong case which has been made for the desirability of synthesis and biological evaluation of naturally occurring nucleosides and nucleotides,[16] synthetic approaches which permit incorporation of a *C*(8)-ribosyl unit or an analogous hydroxylated moiety are worthy of investigation.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on JEOL FX-60 and Varian EM-390, HR-220, and/or HA-100 spectrometers employing tet-

(15) For representative ^{13}C NMR chemical shift values, see: Johnson, L. F.; Jankowski, W. C. "Carbon-13 NMR Spectra"; Wiley-Interscience: New York, 1972.

(16) Kim, S.-H.; Bartholomew , D. G.; Allen, L. B.; Robins, R. K.; Revankar, G. R.; Dea, P. *J. Med. Chem.* 1978, *21*, 883 and references cited therein.

ramethylsilane as an internal standard. Low-resolution mass spectra were obtained on a Varian CH-5 spectrometer. High-resolution mass spectra were obtained on a Varian MAT 731 spectrometer, coupled with a 620i computer and STATOS recorder. The ultraviolet spectra were obtained on a Beckman Acta Model MVI spectrophotometer. Microanalyses were performed by Mr. Josef Nemeth and associates, who also weighed samples for quantitative ultraviolet absorption spectra. The pyridine used in the reactions described below was distilled from barium oxide prior to use. Thin-layer chromatography was carried out on EM silica gel f-254 plates (thickness 0.25 mm). The solvent systems employed were chloroform–ethanol (9:1 to 4:1, v/v) and ethyl acetate–methanol (9:1 to 3:2, v/v).

Ethyl 2-Cyano-2-formamido-4-pentenoate (14a). To a solution of sodium ethoxide (692 mg of Na in 50 mL of absolute ethanol, 30.1 mmol) at 2 °C was added ethyl 2-cyano-2-formamidoacetate (**13a**;[3] 5.15 g, 30.3 mmol). The resulting solution was treated with 3-bromo-1-propene (2.60 mL, 30.0 mmol) in a dropwise fashion and allowed to come to room temperature. The reaction was judged to be complete (pH 7) after 3 h, and solvent was removed in vacuo to give an oily residue. The residue was dissolved in water (20 mL) and extracted with dichloromethane (5 × 15 mL), and the dichloromethane layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oil. Distillation employing a Kugelrohr apparatus [135–145 °C (1.5 mm)] are **14a** as a slightly yellow colored liquid: 5.32 g (90%); ^1H NMR ($(CD_3)_2SO$) δ 1.20 (t, 3, J = 7 Hz, CH_3), 2.75 (br d, 2, CH_2), 4.18 (q, 2, J = 7 Hz, OCH_2), 5.17–5.47 (m, 2, HC=CH_2), 5.57–6.07 (m, 1, HC=CH_2), 8.15 (s, 1, CHO), 9.42 (s, 1, NH); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 40.2 (CH_2), 56.0 (C(2)), 63.8 (CH_3CH_2O), 116.0 (CN), 122.9 (HC=CH_2), 128.2 (HC=CH_2), 161.7 (CHO), 165.4 ($CO_2C_2H_5$). Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.99; H, 6.29; N, 14.26.

Ethyl 2-Acetamido-2-cyano-4-pentenoate (14b). The title compound, **14b**, was prepared according to the method of Albertson[13] and gave the following spectroscopic data: ^1H NMR ($(CD_3)_2SO$) δ 1.20 (t, 3, J = 7 Hz, CH_3), 1.93 (s, 3, CH_3), 2.50–2.93 (m, 2, CH_2), 4.15 (q, 2, J = 7 Hz, OCH_2), 5.17–5.43 (m, 2, HC=CH_2), 5.57–6.03 (m, 1, HC=CH_2), 9.07 (s, 1, NH); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3CH_2), 22.3 ($COCH_3$), 40.3 (CH_2), 56.8 (C(2)), 63.5 (CH_3CH_2O), 116.5 (CN), 122.5 (HC=CH_2), 128.5 (HC=CH_2), 165.9 ($CO_2C_2H_5$), 170.6 ($NHCOCH_3$).

5-Allyl-2,6-diamino-4,5-dihydro-5-formamidopyrimidin-4-one (15a). A solution of sodium ethoxide (235 mg of Na in 30 mL of absolute ethanol, 10.2 mmol) was treated with guanidinium carbonate (918 mg, 5.1 mmol), stirred for 45 min at room temperature, and filtered into a solution of **14a** (2.00 g, 10.2 mmol) in absolute ethanol (50 mL), which was then stirred for 24 h at room temperature. The white precipitate which had formed was collected by filtration, washed with cold absolute ethanol, and dried in vacuo to give homogeneous **15a**: 640 mg (30%); mp 248 °C dec (recrystallized from aqueous ethanol); UV max (0.05 N Na_2HPO_4 buffer) 269 nm (ε 9900), 235 (22 800); ^1H NMR ($(CD_3)_2SO$) δ 2.26–2.30 (m, 2, CH_2), 4.97–5.04 (m, 2, HC=CH_2), 5.49–5.57 (m, 1, HC=CH_2), 8.01 (s, 1, CHO); ^{13}C NMR (CD_3CO_2D) δ 42.8 (CH_2), 59.6 (C(5)), 123.9 (HC=CH_2), 128.1 (HC=CH_2), 159.4, 169.1, 176.4, 178.0; mass spectrum (10 eV), m/e (relative intensity) 209 (M^+, 27), 191 ($M^+ - H_2O$, 10), 181 ($M^+ - CO$, 100), 166 ($M^+ - HNCO$, 7), 141 (21), 140 (70), 139 (23), 112 (12). Anal. Calcd for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.83; H, 5.54; N, 33.70.

5-Acetamido-5-allyl-2,6-diamino-4,5-dihydropyrimidin-4-one (15b), first prepared in this laboratory by Holmes[9] from **14b**, is best obtained in the presence of 1 molar equiv of NaOEt: yield 60%; mp 253 °C dec; UV max (0.05 N Na_2HPO_4 buffer) 269 nm (ε 9900), 235 (22 800); ^1H NMR ($(CD_3)_2SO$) δ 1.82 (s, 3, CH_3), 2.43 (m, 2, CH_2), 5.05 (m, 2, HC=CH_2), 5.50 (m, 1, HC=CH_2); ^{13}C NMR (CD_3CO_2D) δ 21.6 (CH_3), 42.7 (CH_2), 60.6 (C(5)), 123.6 (HC=CH_2), 128.1 (HC=CH_2), 159.2, 169.7, 174.2, 176.8; mass spectrum (10 eV), m/e (relative intensity) 223 (M^+, 100), 180 ($M^+ - HNCO$, 39), 155 (22), 154 (20). Anal. Calcd for $C_9H_{13}N_5O_2 \cdot H_2O$: C, 44.81; H, 6.27; N, 29.03. Found: C, 44.63; H, 6.22; N, 29.43.

5-Allyl-4,5-dihydro-2,5,6-triaminopyrimidin-4-one (23) was obtained free from **15b** after 96 h: yield **36**; mp 238 °C dec; UV max (0.05 N Na_2HPO_4 buffer) 268 nm (ε 7750), 236 (16 950); ^1H NMR (CD_3CO_2D) δ 2.63 (br d, 2, J = 9 Hz, CH_2), 5.07–5.17 (m, 2, HC=CH_2), 5.47–5.93 (m, 1, HC=CH_2); ^{13}C NMR (CD_3CO_2D) δ 46.7 (CH_2), 60.8 (C(5)), 123.2 (HC=CH_2), 129.3 (HC=CH_2), 159.4, 170.0, 178.5; mass spectrum (10 eV), m/e (relative intensity) 181 (M^+, 68), 140 ($M^+ - C_3H_5$, 100), 139 (48), 112 (22), 86 (41). Anal. Calcd for $C_7H_{11}N_5O$: C, 46.40; H, 6.12; N, 38.65. Found: C, 46.67; H, 5.99; N, 38.66.

8-Allyl-2-aminoimidazo[1,5-a]-1,3,5-triazin-4(3*H*)-one (17). A suspension of **15a** (52 mg, 0.25 mmol), dry pyridine (5 mL), and chlorotrimethylsilane (95 μL, 0.75 mmol) was stirred for 20 min at room temperature. Hexamethyldisilazane (160 μL, 0.75 mmol) was added, and the resulting mixture was heated at reflux for 3 min. When the mixture cooled, the solvents were removed in vacuo, the residue was treated with absolute methanol (5 mL), and the resulting solution was stirred for 45 min at room temperature. The methanolic solution was concentrated under reduced pressure, and the resulting white solid was dried in vacuo to give homogeneous **17**: 45 mg (95%); mp >110 °C dec; ^1H NMR ($(CD_3)_2SO$) δ 3.20–3.30 (m, 2, CH_2), 4.83–5.10 (m, 2, HC=CH_2), 5.67–6.13 (m, 1, HC=CH_2), 6.43 (br, 2, NH_2), 7.90 (s, 1, 6-H); ^{13}C NMR ($(CD_3)_2SO$) δ 30.1 (CH_2), 114.9 (HC=CH_2), 121.5, 124.1 (C(6)), 133.2, 136.8 (HC=CH_2), 144.6, 148.3; mass spectrum (10 eV), m/e (relative intensity) 191 (M^+, 100), 190 (18), 164 ($M^+ - HCN$, 13), 147 (46), 85 (46); high-resolution mass spectrum, m/e 191.0809 (calcd for $C_8H_9N_5O$).

The preparation of **8-allyl-2-amino-6-methylimidazo[1,5-a]-1,3,5-triazin-4(3*H*)-one (20)** requires a heating period of 4 h at reflux in pyridine: yield 82%; mp >120 °C dec (precipitated from methanol); UV max (CH_3CN) 264 nm (ε 11 950); ^1H NMR ($(CD_3)_2SO$) δ 2.60 (s, 3, CH_3), 3.20 (m, 2, CH_2), 4.90–5.10 (m, 2, HC=CH_2), 5.90 (ddt, 1, J = 17, 10, 7 Hz, HC=CH_2), 6.20 (br, 2, NH_2); ^{13}C NMR ($(CD_3)_2SO$) δ 15.9 (CH_3), 30.0 (CH_2), 114.7 (HC=CH_2), 119.2, 133.2, 135.0, 136.9 (HC=CH_2), 146.0, 147.4; mass spectrum (10 eV), m/e (relative intensity) 205 (M^+, 100), 204 (8), 164 ($M^+ - C_2H_3N$, 11), 163 (21), 148 (11), 147 (81); high-resolution mass spectrum, m/e 205.0966 (calcd for $C_9H_{11}N_5O$). Anal. Calcd for $C_9H_{11}N_5O \cdot 0.75H_2O$: C, 49.42; H, 5.76; N, 32.02. Found: C, 49.23; H, 5.52; N, 32.14.

2-Amino-8-propylimidazo[1,5-a]-1,3,5-triazin-4(3*H*)-one. To a solution of **17**, prepared from **15a** (209 mg, 1 mmol) as described above, in ethanol (60 mL) was added 10% Pd/C (200 mg). The mixture was hydrogenated at 3 atm of H_2 for 15 h and filtered through Celite. Concentration of the filtrate in vacuo gave the propyl derivative as a white, homogeneous solid (175 mg, 91%) with the same R_f values as **17** on silica gel TLC in several solvent systems: mp >170 °C dec; ^1H NMR ($(CD_3)_2SO$) δ 0.87 (t, 3, J = 6 Hz, CH_3), 1.57 (m, 2, CH_2), 2.50 (overlaps with $(CD_3)_2SO$, 2,8-CH_2), 6.50 (br, 2, NH_2), 7.83 (s, 1, 6-H); mass spectrum (35 eV), m/e (relative intensity) 193 (M^+, 52), 178 ($M^+ - CH_3$, 6), 165 ($M^+ - C_2H_4$, 24), 164 ($M^+ - C_2H_5$, 100), 122 ($M^+ - C_2H_5 - CH_2N_2$, 15); high-resolution mass spectrum (10 eV), m/e 193.0965 (calcd for $C_8H_{11}N_5O$), 164.0572 ($C_6H_6N_5O$), 122.0354 ($C_5H_4N_3O$).

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Registry No. 13a, 1759-25-7; **13b**, 4977-62-2; **14a**, 78109-14-5; **14b**, 5424-14-6; **15a**, 78109-15-6; **15b**, 78109-16-7; **17**, 78109-17-8; **20**, 78109-18-9; **23**, 78109-19-0; 3-bromo-1-propene, 106-95-6; guanidinium carbonate, 124-46-9; 2-amino-8-propylimidazo[1,5-a]-1,3,5-triazin-4(3*H*)-one, 78109-20-3.