viously.[18] The Boc group was removed by treating with 20% trifluoroacetic acid in methylene chloride.

The mixed anhydride **15** was prepared according to the following procedure. **9** (0.169 g, 0.0005 mol) was dissolved in 20 ml of dry DMSO with warming. To the cooled solution was added 20 ml of dry tetrahydrofuran, followed by 0.063 g (0.000625 mol) of *N*-methylmorpholine. The mixture was chilled in an ice bath for 15 min, 0.068 g (0.0005 mol) of freshly distilled isobutylchloroformate was added, and the formation of the mixed anhydride allowed to proceed for an additional 15 min in the ice bath. The solution was then added to the resin-bound glutamic acid α-benzyl ester. After 18 hr at room temperature, the reaction mixture was filtered and the resin washed two times with DMSO and three times with 30-ml portions of *p*-dioxane.

B. Deprotection, Cleavage, and Purification. A mixture of 15 ml of 2 *N* NaOH and 15 ml of purified dioxane was deaerated by bubbling N_2 for 10 min. The resin-bound product was shaken vigorously with this mixture for 1 hr at room temperature in a closed reaction vessel. The vessel was placed in a water bath at 50° for 20 min. After being cooled to room temperature, the mixture was filtered and the filtrate diluted to ~400 ml with H_2O and then adjusted to pH 7. The solution was further diluted to 1 l. and applied to a 5 × 10 cm DEAE column. The column was washed with distilled water and the products were obtained by discharging the resin with 0.5 *M* NH_4OH. The ammonia was driven off *in vacuo* and the ammonium salt of **1** repurified by chromatography on a standard DEAE Cl^- column with the linear sodium chloride gradient described earlier. A small amount of isofolic acid (**2**) was obtained and identified by comparison with an authentic sample. Pure **1** thus obtained showed the following uv absorptions: λ max (0.1 *N* NaOH) 413 nm (ε 5849), 269 (23,729), 248 (23,376); λ max (0.1 *N* HCl) 402 nm (ε 6466) and 260 (28,736). *Anal.* ($C_{19}H_{20}N_8O_5 \cdot 0.5H_2O$) C, H, N, O.

Reduction of 1 with Dithionite. **1** (5 mg) was dissolved in 25 ml of H_2O by the addition of 0.1 *N* NaOH so that the pH reached 10. This solution was slowly heated to 50° and 50 mg of sodium dithionite was added in small portions. The solution became colorless after 5 min. The uv spectrum of an aliquot of this solution showed the disappearance of the absorption at 413 nm. The pH of the solution was adjusted to 3 and after 10 min readjusted to 8. The solution was then filtered, 500 mg of MnO_2 was added, and the reaction mixture was stirred for 16 hr in an open beaker. After removal of MnO_2 by filtration, the compound was chromatographed on a 1.4 × 31 cm DEAE Cl^- column. Two peaks were eluted from the column and the more polar one was identified as **1**. The less polar material which eluted at a NaCl concentration of 0.185 *M* was the dihydro compound as evidenced by its uv spectrum in 0.1 *N* NaOH [λ max 320 (sh) and 290 nm] and also by reoxidation to **1**. No other uv-absorbing material was eluted from the column.

Acknowledgments. This work was supported by Grant No. CI-86N of the American Cancer Society and NIH Grant 1-RO1-CA-16048. The technical assistance of Miss Pay Taylor and Miss Eleanor Braverman is gratefully acknowledged.

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Pyrimido[4,5-*c*]isoquinolines. 2. Synthesis and Biological Evaluation of Some 6-Alkyl-, 6-Aralkyl-, and 6-Aryl-1,3-diamino-7,8,9,10-tetrahydropyrimido[4,5-*c*]isoquinolines as Potential Folate Antagonists[1,†]

Andre Rosowsky* and Nickolas Papathanasopoulos

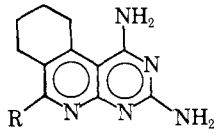
The Children's Cancer Research Foundation and the Department of Biological Chemistry, Harvard Medical School, Boston, Massachusetts 02115. *Received June 3, 1974*

1,3-Diamino-7,8,9,10-tetrahydropyrimido[4,5-*c*]isoquinolines with lipophilic alkyl, aralkyl, or aryl substituents at position 6 were synthesized *via* a method involving (1) condensation of 2-acyl- or 2-aroylcyclohexanones with cyanoacetamide in the presence of a secondary amine, (2) chlorination of the resultant 4-cyano-3-hydroxy-5,6,7,8-tetrahydroisoquinolines with phenylphosphonic dichloride, and (3) reaction of the chloronitriles with guanidine carbonate in refluxing *N,N*-dimethylformamide. An alternative approach was also discovered when 3-amino-4-cyano-5,6,7,8-tetrahydroisoquinoline proved to undergo ring closure directly on treatment with guanidine carbonate in boiling 1-octanol. The products were potent inhibitors of folate-dependent *Streptococcus faecium* ATCC 8043 and purified dihydrofolate reductase from *Lactobacillus casei* ATCC 7469 when bulky lipophilic groups were present at position 6.

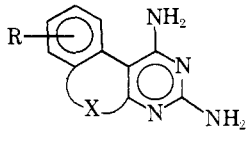
As part of our research program on tricyclic 2,4-diaminopyrimidines as folate antagonists and potential cancer chemotherapeutic agents,[2] it was of interest to prepare some 1,3-diamino-7,8,9,10-tetrahydropyrimido[4,5-*c*]isoquinolines of general structure **1** and to evaluate the biological activity of these compounds with reference to other angular condensed 2,4-diaminopyrimidine types studied previously in our laboratory, such as the bridged pyrimethamine analogs **2**[3-7] and the thieno[2,3-*d*]pyrimidines

†This investigation was supported in part by Research Grant C6516 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

3.[8,9] Compounds of structure 1 with strongly hydrophobic R substituents were especially attractive because of the finding that biological activity is enhanced in the 1,3-diaminobenzo[*f*]quinazoline series when long-chain alkyl substitution is introduced at position 6.[10]



1



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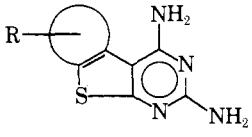
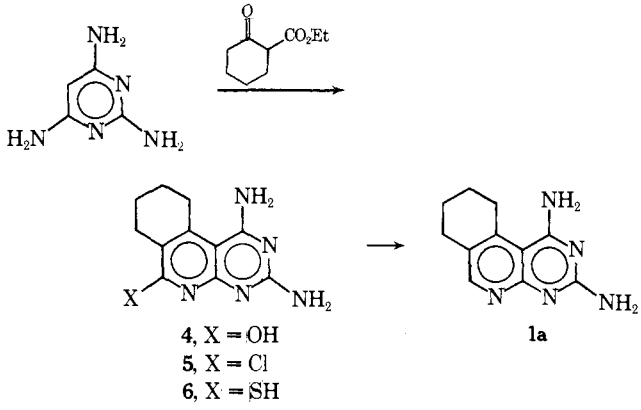


3

Chemistry. A search of the literature revealed that 1,3-diamino-7,8,9,10-tetrahydropyrimido[4,5-*c*]isoquinoline (**1a**) itself, the parent and sole reported member of the series until now, was obtained some time ago by Hitchings and coworkers[10-13] as part of a larger investigation dealing primarily with bicyclic rather than tricyclic compounds.



4, X = OH
5, X = Cl
6, X = SH

1a

The synthesis of **1a** was achieved by condensation of 2,4,6-triaminopyrimidine with 2-carbethoxycyclohexanone, followed by chlorination with phosphorus oxychloride, thiation with sodium hydrosulfide, and dethiation with Raney nickel (**4** → **5** → **6** → **1a**).

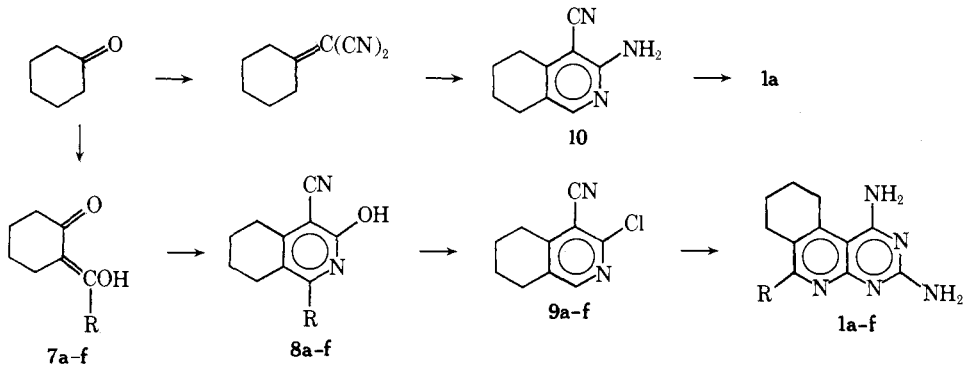
Since the foregoing synthesis appeared to be inherently unsuited to the preparation of pyrimido[4,5-*c*]isoquinolines with alkyl, aralkyl, or aryl substitution at position 6, a new route was developed which permitted the synthesis of the 6-substituted congeners **1b-f** (Table I). The reaction sequence leading to these products is depicted in Scheme I.

Condensation of the 1,3-diones **7b-f** with cyanoacetamide in ethanol containing *N,N*-diethylamine as a base catalyst[14] afforded the 4-cyano-3-hydroxy-5,6,7,8-tetrahydroisoquinolines **8b-f**. Yields were 70-85% in the formation of isoquinolines **8b**, **8c**, and **8e** but fell significantly with isoquinolines **8d** (18%) and **8f** (41%), probably because of decreased reactivity of the 1,3-dione system. In compound **7d** there is the possibility of enolization of the side-chain carbonyl group preponderantly in the wrong direction (*i.e.*, toward the phenyl ring), whereas in compound **7f** the low yield is attributable to the deactivating inductive effect of the aromatic halogen substituent. Chlorination of the 4-cyano-3-hydroxy-5,6,7,8-tetrahydroisoquinolines **8b-f** was effected in high yield by treatment with refluxing phosphorus oxychloride or treatment with excess phenylphosphonic dichloride[15] at 160° without solvent for 2.5-3.0 hr. The physical constants of the hydroxy derivatives **8b-f** and chloro derivatives **9b-f** are shown in Table II. Infrared and ultraviolet spectral evidence supported the conclusion that compounds **8b-f** exist predominantly in the isoquinolin-3(2*H*)-one tautomeric form (intense amide ir absorption *ca.* 1630 cm^{-1}).

The 3-chloro-4-cyano-5,6,7,8-tetrahydroisoquinolines **9b-f** were converted into the corresponding pyrimido[4,5-*c*]isoquinolines **1b-f** by reaction with excess guanidine carbonate in refluxing *N,N*-dimethylformamide for 1.0-3.0 hr. The products were obtained in approximately 20-40% yield as yellow microcrystalline solids showing the expected high melting point and limited solubility in organic solvents. Analytically pure specimens were obtained in most instances by digestion of the crude product with hot ethanol (in order to remove unchanged starting material and other impurities) and a single recrystallization from *N,N*-dimethylformamide. Compound **1e** was sufficiently soluble in ethanol to allow effective purification by column chromatography on Florisil with ethanol as the eluent. With compound **1f** purification was achieved *via* the hydrochloride salt **1f**·HCl, which was likewise sufficiently ethanol-soluble to permit use of this solvent for recrystallization. Physical constants of the pyrimido[4,5-c]isoquinolines prepared in this manner are shown in Table I.

2-Hydroxymethylenecyclohexanone (**7a**) is said to yield 3-cyano-2-hydroxy-5,6,7,8-tetrahydroquinoline rather than

Scheme I



10

7a-f

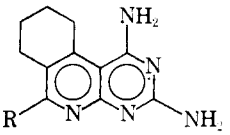
8a-f

9a-f

1a-f

a, R = H
b, R = Me
c, R = Et
d, R = $CH_2C_6H_5$
e, R = C_6H_5
f, R = C_6H_4-*p*-Cl

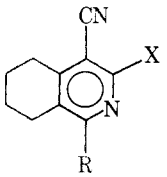
Table I. Physical Constants of 1,3-Diamino-7,8,9,10-tetrahydropyrimido[4,5-c]isoquinolines



Compd	R	Yield, %	Mp, °C dec	Empirical formula	Analyses
1a	H	38	>340	$C_{11}H_{13}N_5$	C, H, N
1b	CH_3	40	319–320	$C_{12}H_{15}N_5 \cdot 0.25H_2O$	C, H, N
1c	C_2H_5	23	323–325	$C_{13}H_{17}N_5$	C, H, N
1d	$CH_2C_6H_5$	38	244–246	$C_{18}H_{19}N_5 \cdot 0.5H_2O$	C, H, N
1e	C_6H_5	18	300–305	$C_{17}H_{17}N_5$	C, H, N
1f	C_6H_4-*p*-Cl	*a*	295–300	$C_{17}H_{16}ClN_5$	C, H, Cl, N
1f·HCl	C_6H_4-*p*-Cl	27	>340	$C_{17}H_{16}ClN_5 \cdot HCl$	C, H, Cl, N

[a]Cyclization yield based on isolation of the product as the hydrochloride salt 1f·HCl.

Table II. Physical Constants of 5,6,7,8-Tetrahydroisoquinolines



Compd	X	R	Yield, %	Mp, °C[a]	Empirical formula	Analyses
8a	OH	H	19	256–258[b]		
8b	OH	CH_3	85	>360 dec[c]		
8c	OH	C_2H_5	74	325–328 dec	$C_{12}H_{14}N_2O$	C, H, N
8d	OH	$CH_2C_6H_5$	18	253–255 dec[d]	$C_{17}H_{16}N_2O$	C, H, N
8e	OH	C_6H_5	70	335–338 dec	$C_{16}H_{14}N_2O$	C, H, N
8f	OH	C_4H_4-*p*-Cl	41	325–328 dec	$C_{16}H_{13}ClN_2O$	C, H, Cl, N
9a	Cl	H	96	132–134[e]		
9b	Cl	CH_3	76	98–99[f]		
9c	Cl	C_2H_5	92	77–79	$C_{12}H_{13}ClN_2$	C, H, Cl, N
9d	Cl	$CH_2C_6H_5$	~100[g]	73–74	$C_{17}H_{15}ClN_2$	C, H, Cl, N
9e	Cl	C_6H_5	86	172–174	$C_{16}H_{13}ClN_2$	C, H, Cl, N
9f	Cl	C_6H_4-*p*-Cl	~100[g]	108–109	$C_{16}H_{12}Cl_2N_2$	C, H, Cl, N
10	NH_2	H	38	194–196[h]		

[a]Compounds 8a–f, 9b–d, and 9f were recrystallized from EtOH; 9a was used without recrystallization; 9e was sublimed twice at 150–155° (0.5 mm); 10 was recrystallized from benzene. [b]Lit.[16] mp 249°. [c]Lit.[14] mp 357–359° dec. [d]Lit.[29] mp 245–248° (AcOH). [e]Lit.[21] mp 134–135°. [f]Lit.[14] mp 100–100.5°. [g]Crude yield of material used directly in the next step. [h]Mp 193–194°: E. C. Taylor and J. Klug, unpublished results.

the isomeric compound 4-cyano-3-hydroxy-5,6,7,8-tetrahydroisoquinoline (8a) on reaction with cyanoacetamide and *N,N*-diethylamine.[16] Moreover, the condensation product in the reaction of 7a with 4-amino-2,6-dihydroxypyrimidine in hot polyphosphoric acid has been formulated arbitrarily as the linear compound 2,4-dihydroxy-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline.[17] Although we were aware of a variant of these reactions wherein the use of 2-aminomethylenecyclohexanone in place of 7a allegedly brings about a reversal in direction of ring closure,[18,19] we chose not to follow this enamine approach but to take advantage instead of a facile and entirely unambiguous synthesis relying on the condensation of cyclohexylidenemalononitrile with ethyl orthoformate and ammonia which was developed by Taylor.[20,‡] The aminonitrile generated *via* this route must necessarily have the isoquinoline structure 10 by virtue of its mechanism of formation and is known to differ from the isomeric quinolineaminonitrile derived from 2-hydroxymethylenecyclohexanone on successive reaction with malononitrile and ammonia.[21] While our original plan had been to convert 10 into the corresponding 3-hydroxy derivative 8a and proceed *via* the general sequence in Scheme I, we were rewarded with the finding that aminonitrile 10 actually undergoes *direct* annelation to 1a in 38% yield on treatment with guanidine carbonate in refluxing 1-octanol. This procedure constitutes an attractive and quite practical alternative to the literature synthesis of 1a, which entails an experimentally troublesome thiation and dethiation sequence.[10-12] The formulation of 10 as an isoquinoline requires that the ensuing product, 1a, have the assigned angular pyrimido-[4,5-*c*]isoquinoline structure.

With compound 1a in hand *via* unequivocal isoquinoline intermediate 10, it became of interest to ascertain whether the reaction of 7a with cyanoacetamide does indeed yield 3-cyano-2-hydroxy-5,6,7,8-tetrahydroquinoline

‡The experimental procedure for the synthesis of aminonitrile 10 was kindly provided by Professor E. C. Taylor, Princeton University, and will be reported by him in a forthcoming paper (personal communication).

Table III. Bacterial and Enzyme Inhibition by 1,3-Diamino-7,8,9,10-tetrahydropyrimido[4,5-*c*]isoquinolines

Compd	Substitution	*S. faecium*, ID_{50}, $\mu g/ml$[b]	Dihydrofolate reductase,[a] ID_{50}, mol/l.
1a	6-H	1.0*	
1b	6-Me	0.03	
1c	6-Et	0.01	
1d	6-$CH_2C_6H_5$	0.0001*	1×10^{-7}
1e	6-C_6H_5	0.001*	1×10^{-5}
1f	6-C_6H_4-*p*-Cl	0.001*	1×10^{-6}

[a]Enzyme derived from *L. casei* ATCC 7469 was provided by Dr. R. L. Kisliuk, Tufts-New England Medical Center. [b]Folate concentration = 0.001 $\mu g/ml$.

as claimed.[16] Accordingly, this substance was synthesized as prescribed[16] and then chlorinated with phenylphosphonic dichloride. Reaction of the resultant chloronitrile with guanidine carbonate in boiling *N,N*-dimethylformamide gave a product (38% yield) which proved to be indistinguishable from the product originating from isoquinoline **10** with respect to melting point, solubility properties, tlc mobility, and infrared and ultraviolet spectra. We conclude on the basis of this evidence that the product of base-catalyzed condensation of **7a** with cyanoacetamide[16] should be reformulated as 4-cyano-3-hydroxy-5,6,7,8-tetrahydroisoquinoline (**8a**) and that the chlorination product previously regarded as 2-chloro-3-cyano-5,6,7,8-tetrahydroquinoline[22] must in fact be 3-chloro-4-cyano-5,6,7,8-tetrahydroisoquinoline (**9a**). A similar structural reassignment has been made recently[14] for the adduct of **7b** and cyanoacetamide, which was also once considered to be a quinoline.[16]

Biological Results. Compounds prepared in this work were assayed for growth inhibitory activity against the folate-requiring microorganism *Streptococcus faecium* ATCC 8043 as previously described.[23] Activities are shown in Table III as ID_{50} values in $\mu g/ml$ at a folate concentration of 0.001 $\mu g/ml$. Whereas 1,3-diamino-7,8,9,10-tetrahydropyrimido[4,5-*c*]isoquinoline (**1a**) itself was essentially inactive in this test system, a substantial enhancement of growth inhibitory potency was observed when a lipophilic substituent was introduced at position 6. Although the 6-methyl derivative **1b** and 6-ethyl derivative **1c** were only some 30–100 times more active than **1a**, when the 6-substituent was benzyl (**1d**) or aryl (**1e,f**) the activity relative to **1a** rose by more than three orders of magnitude.

Also shown in Table III are the ID_{50} values for compounds **1d–f** against purified dihydrofolated reductase derived from *Lactobacillus casei*. The assays were performed according to a standard procedure.[24] The most effective inhibitor proved to be the 6-benzyl derivative **1d**. The antibacterial and enzyme inhibition data suggest that binding of the pyrimido[4,5-*c*]isoquinoline ring system to dihydrofolate reductase occurs in such a way as to allow bulky lipophilic substituents at position 6 to form strong hydrophobic bonds to the enzyme. Similar conclusions have been reached by Hurlbert and coworkers[13] relative to the binding of pyrido[2,3-*d*]pyrimidines with lipophilic substituents in the pyridine moiety to dihydrofolate reductases of various species origin.

Compounds **1b–e** were also evaluated for experimental antitumor activity against L1210 leukemia and P388 leukemia in BDF/1 hybrid mice and P1534 leukemia in DBA/2 inbred mice.[25] Daily intraperitoneal injections were given for 4 days beginning one day after tumor implantation with 10^5 cells. In preliminary experiments, compound **1b** gave marginal increases in mean survival of 19% against the L1210 tumor and 29% against the P1534 tumor at doses of 125 mg/kg, although there was appreciable weight loss due to toxicity. Compounds **1c** and **1e** were likewise toxic and afforded no significant prolongation in life span with these two tumors. Compound **1d**, against the P388 tumor, produced a 27% increase in survival at a dose of 160 mg/kg, with some toxicity noted once again.

Experimental Section§

Preparation of 1,3-Diones. 2-Acetylcyclohexanone (**7b**) was obtained from cyclohexanone, EtOAc, and Ac_2O *via* the boron trifluoride procedure of Hauser and coworkers.[26] 2-Hydroxymethylenecyclohexanone (**7a**) and the other 1,3-diones were prepared from the piperidine enamine of cyclohexanone according to the method of Stork and coworkers.[27] The procedure described for compound **7f** in the following experiment is typical of the enamine reactions. All the 1,3-diones were known compounds: **7a**,[27] **7b**,[26] **7c**,[28] **7d**,[29] **7e**,[30] and **7f**.[31]

2-(*p*-Chlorobenzoyl)cyclohexanone (7f). A solution of 1-piperidinocyclohexene (95 g, 0.57 mol) and dry dioxane (1 l.) was treated with Et_3N (58 g, 0.57 mol) and *p*-chlorobenzoyl chloride (100 g, 0.57 mol), then stirred mechanically under reflux overnight, cooled, and filtered. The solid was washed with CH_2Cl_2 and the combined filtrate and wash solution were returned to the reaction flask, treated with 10% HCl (200 ml), and refluxed for 2 hr. Most of the solvent was removed by distillation, water (200 ml) was added, and the product was extracted into CH_2Cl_2. The organic extracts were washed with 5% $KHCO_3$, dried over $MgSO_4$, and evaporated under reduced pressure. The residue (58 g, 42% yield) was a pale yellow solid. Recrystallization from EtOH (charcoal) gave long colorless needles, mp 88–89° (lit.[31] mp 91.5–92°).

Reactions of 1,3-Diones with Cyanoacetamide. A. 4-Cyano-3-hydroxy-5,6,7,8-tetrahydroisoquinoline (8a). A mixture of **7a** (63 g, 0.050 mol), cyanoacetamide (63 g, 0.075 mol), Et_2NH (50 ml), and EtOH (400 ml) was heated until a clear solution was obtained and then stirred at room temperature overnight. Filtration and washing with EtOH and then CH_2Cl_2 gave a colorless solid (17 g).

B. 4-Cyano-1-ethyl-3-hydroxy-5,6,7,8-tetrahydroisoquinoline (8c). A mixture of **7c** (7.0 g, 0.046 mol), cyanoacetamide (3.9 g, 0.046 mol), 25% aqueous Me_2NH (5 ml), and EtOH (150 ml) was stirred at room temperature for 48 hr. Filtration, thorough washing with CH_2Cl_2, and drying under reduced pressure left a colorless solid (6.8 g).

Chlorination of Hydroxynitriles. A. 3-Chloro-4-cyano-1-phenyl-5,6,7,8-tetrahydroisoquinoline (9e). A mixture of **8e** (2.5 g, 0.0097 mol) and phenylphosphonic dichloride (12 g) was heated at 160° (internal temperature) for 3 hr and then cooled, poured into ice–water, and stirred for 15 min. Neutralization with concentrated ammonia, filtration, thorough washing with cold water, and drying under reduced pressure gave a colorless solid (2.3 g).

B. 3-Chloro-4-cyano-1-methyl-5,6,7,8-tetrahydroisoquinoline (9b). A mixture of **8b** (12 g, 0.065 mol) and $POCl_3$ (200 ml) was refluxed for 4 hr, cooled, poured into ice–water, and stirred for 30 min. The work-up described in the preceding experiment was followed, but in addition the crude product was extracted with $CHCl_3$ in order to remove a small quantity of insoluble starting material. Evaporation of the $CHCl_3$ extracts left a colorless solid (12 g).

Condensations with Guanidine. 1,3-Diamino-7,8,9,10-tetrahydropyrimido[4,5-*c*]isoquinoline (1a). A. A mixture of aminonitrile **10** (40 g, 0.23 mol)[20,‡] and guanidine carbonate (40 g, 0.44 equiv) in 1-octanol (300 ml) was stirred under reflux for 30 min, cooled to room temperature, diluted with EtOH (200 ml), and filtered. The solid was washed thoroughly with hot EtOH, dissolved in dilute HCl, reprecipitated by basification with ammonia, filtered, washed with water and hot EtOH, and dried (19

§Ultraviolet spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Ir spectra were taken in KCl disks with a Perkin-Elmer Model 137B double-beam recording spectrophotometer. Melting points were measured in Pyrex capillary tubes in a Mel-Temp apparatus (Laboratory Devices, Inc., Cambridge, Mass.) and are uncorrected. Microanalyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn., and are within ±0.4% of theory except where otherwise noted.

g). For microanalysis, a portion of this material was digested once more with boiling EtOH and then crystallized twice from *N,N*-dimethylformamide and dried at 90° (0.05 mm) for 24 hr: uv λ_{max} (EtOH) 226 nm (ϵ 27,920), 246 (25,240), 270.5 (9540), 350 (9400); λ_{max} (pH 1) 225 nm (ϵ 36,360), 263 infl (7090), 324 (13,510), 336 (12,262). Refrigeration of the combined 1-octanol mother liquor and EtOH washings led to the recovery of some unchanged **10** (11 g, 28%).

B. Synthesis of 1a *via* the Chloronitrile Route. A mixture of **9a** (18 g, 0.093 mol), guanidine carbonate (18 g), and *N,N*-dimethylformamide (100 ml) was stirred under reflux for 1.5 hr, cooled, diluted with CH_2Cl_2, and filtered. After being washed thoroughly with CH_2Cl_2 and dried under reduced pressure, the solid was digested with 10% HCl (250 ml), the insoluble portion was filtered off, and the filtrate was basified with 5% KOH. Filtration, washing to neutrality with water, extraction with several portions of boiling hot EtOH, and drying under reduced pressure left a yellow solid. Infrared spectra and quantitative ultraviolet absorption spectra of this product and of the material prepared in the preceding experiment were essentially indistinguishable, and both compounds showed the same mobility on silica gel tlc sheets (Eastman 6060 chromagram with fluorescent indicator, 4:1 C_6H_6–MeOH, R_f 0.4).

1,3-Diamino-6-benzyl-7,8,9,10-tetrahydropyrimido[4,5-*c*]isoquinoline (1d). A mixture of **9d** (1.5 g, 0.0051 mol) and guanidine carbonate (1.5 g) was stirred in *N,N*-dimethylformamide (20 ml) under reflux for 3 hr. The solid was collected, washed with CH_2Cl_2, dried under reduced pressure, and digested with hot 10% HCl. The insoluble portion was filtered off and the filtrate was basified with ammonia. The precipitated product was collected, washed thoroughly with water, and dried (0.6 g).

Acknowledgment. The authors are indebted to the following colleagues at The Children's Cancer Research Foundation for the biological data reported in this paper: Dr. George E. Foley and Mr. Harold Riley, *S. faecium* data; Ms. Barbara Brown, experimental mouse tumor data; Dr. M. H. N. Tattersall and Ms. Catherine Widiger, enzyme inhibition data. Helpful correspondence from Professor Edward C. Taylor, Department of Chemistry, Princeton University, is also acknowledged with pleasure.

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