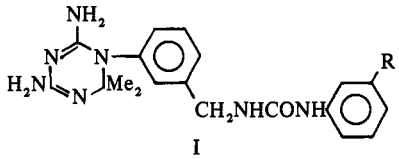
Irreversible Enzyme Inhibitors. 198.†,‡ Diaminodihydro-*s*-triazines and Diaminopyrimidines Bearing Substituted (Ureidomethyl)phenyl Substituents as Reversible Inhibitors of Dihydrofolate Reductase

Wallace T. Ashton,*,§ Larry L. Kirk,* and B. R. Baker#

Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California 93106. *Received November 20, 1972*

Based on the activity of 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-[*m*-(*m*-fluorosulfonylphenylureidomethyl)phenyl]-*s*-triazine (**1**) against murine leukemia L1210, several related reversible inhibitors of dihydrofolate reductase were prepared. These consisted of triazines bearing *m*-(arylureidomethyl)phenyl (I) or *m*-(*N,N*-dialkylureidomethyl)phenyl (II) substituents and pyrimidines bearing the *p*-(arylureidomethyl)phenyl group (III). Some of the triazines (I) approached the activity of **1** *in vitro*. The potency of the pyrimidines (III) against L1210 cell culture was greatly enhanced by small, electron-withdrawing meta substituents on the terminal ring, and the *m*-NO_2 compound **14** was 2000-fold more inhibitory than than **1**.

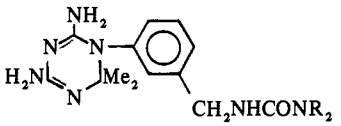
A number of substituted 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-phenyl-*s*-triazines which are reversible or irreversible inhibitors of dihydrofolate reductase have shown excellent *in vivo* activity against Walker carcinosarcoma 256 and Dunning leukemia in the rat.[1,2] For unknown reasons, very few compounds of this class were significantly active *in vivo* against L1210 mouse leukemia. One inhibitor showing definite activity in the L1210 screen is **1** (I, R = SO_2F)[3] which gave a 66% increase in survival time at optimum dosage (100 mg/kg/day). Although **1** contains a terminal



I

sulfonyl fluoride group, it does not inactivate dihydrofolate reductase from L1210,[3] so its antileukemic effect cannot be attributed to irreversible inhibition. This prompted the investigation of a series of analogs of type I (Table I) in which the sulfonyl fluoride was replaced by other R groups. It was hoped that suitable modifications could lead to improvements in reversible enzyme inhibition and cell membrane transport.

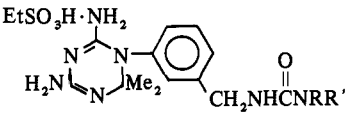
In several series of triazines containing an amide side chain, it was found that replacement of a terminal carboxanilide moiety by *N,N*-dialkylcarboxamide sometimes increased *in vitro* and/or *in vivo* activity.[1] Consequently, two *N,N*-dialkylureas of type II were prepared and evaluated (Table I).



II, R = alkyl

As part of an investigation of diaminopyrimidine analogs of active diaminodihydro-*s*-triazines,** we were interested in the pyrimidine counterparts of **1**. Although the directly analogous compounds were not readily accessible, the availability of **10**[4] allowed the preparation of a series of pyrimidines having a *p*-(phenylureido)methyl side chain (III) (Table II).

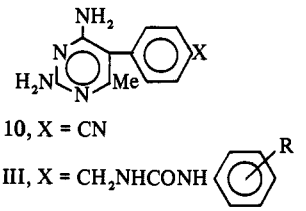
Table I. Inhibition of Dihydrofolate Reductase and L1210 Cell Culture by



No.	NRR'	Enzyme source[a]	I_{50},[b] μM	ED_{50},[c] μM	ED_{50}/I_{50}[d]
1[e]	$NHC_6H_4SO_2F$-*m*	L1210/FR8	0.066	0.13	2
2	NHC_6H_5	L1210/DF8	0.030	0.3	10
3	NHC_6H_4Cl-*m*	L1210/DF8	0.0090	1.5	170
4	NHC_6H_4OMe-*m*	L1210/DF8	0.0095	2	200
5	$NHC_6H_4NO_2$-*m*	L1210/DF8	0.0080	0.8	100
6	NHC_6H_4CN-*m*	L1210/DF8	0.0064	6	1000
7	$NHC_6H_4CONMe_2$-*m*	L1210/DF8	0.017	60	4000
8	NEt_2	L1210/DF8	0.78	>100	>100
9	c-$N(CH_2CH_2)_2O$	L1210/DF8	0.37	>100	>300

[a] L1210/FR8 and L1210/DF8 are two amethopterin-resistant strains of L1210 mouse leukemia. [b] Concentration for 50% reversible inhibition when assayed with 6 μ*M* dihydrofolate, 30 μ*M* NADPH, and 0.15 *M* KCl in pH 7.4 Tris buffer as previously described: B. R. Baker, G. J. Lourens, R. B. Meyer, Jr., and N. M. J. Vermeulen, *J. Med. Chem.*, 12, 67 (1969) (paper 133). [c] Concentration for 50% inhbition of L1210 cell culture. [d] An approximation of membrane transport (see reference in footnote *b*). [e] Enzyme inhibition data from ref 3.

Biological Evaluation. The inhibitory effects of triazines of types I and II on dihydrofolate reductase and against



L1210 cell culture are shown in Table I. The new *N*-phenylureido derivatives **2-7** were all excellent reversible inhibitors of L1210 dihydrofolate reductase and, in the case of **6**, as much as an order of magnitude more potent than the lead compound **1**.†† Both hydrophobic and polar substituents were well tolerated from the standpoint of enzyme binding.

Several of these analogs were moderately potent inhibitors of growth of L1210 cells in culture, the most effective being the unsubstituted (**2**) and *m*-NO_2 (**5**) derivatives. None, however, were quite as active as **1** in this test system. The *m*-dimethylcarbamoyl substituent of **7** apparently has a par-

†This work was generously supported by Grant CA-08695 from the National Cancer Institute, U. S. Public Health Service.

‡For the previous paper in this series, see Baker and Ashton.[1]

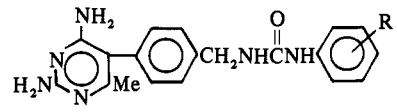
§Department of Pharmaceutical Chemistry, College of Pharmacy, Medical University of South Carolina, Charleston, S. C. 29401.

#Deceased Oct 1971.

**B. R. Baker and L. L. Kirk, unpublished results.

††The comparison is only approximate, since 1 was tested on dihydrofolate reductase from another strain of L1210.

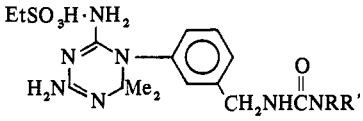
Table II. Inhibition of Dihydrofolate Reductase and L1210 Cell Culture by



No.	R	I_{50},[a] μM	ED_{50},[b] μM	ED_{50}/I_{50}[c]
11	H	0.032	0.40	13
12	3-Cl	0.020	0.00016	0.008
13	3-OMe	0.015	0.70	47
14	3-NO_2	0.010	0.000061	0.006
15	3-CN	0.022	0.00076	0.035
16	3-$CONMe_2$	0.012	0.09	8
17	3-Me-4-SO_2F	0.010[d]	0.20	20

[a]L1210/DF8 dihydrofolate reductase; see footnotes *a* and *b*, Table I. [b]See footnote *c*, Table I. [c]See footnote *d*, Table I. [d]Also gave 20% irreversible inhibition after 1 hr when a concentration of 0.05 μM was incubated with enzyme at 37° in Tris buffer (pH 7.4) containing 30 μM NADPH.

Table III. Physical Constants of



No.	NRR′	Method	Yield,[a] %	Mp, °C dec	Formula[b]
2	NHC_6H_5	B[c]	28[d]	>145[e,f]	$C_{21}H_{29}N_7O_4S$
3	NHC_6H_4Cl-*m*	B	46[d]	>140[e]	$C_{21}H_{28}ClN_7O_4S$
4	NHC_6H_4OMe-*m*	B[c,g]	15[d]	>150[e]	$C_{22}H_{31}N_7O_5S \cdot 0.75C_3H_8O$
5	$NHC_6H_4NO_2$-*m*	B	34[d]	>140[e]	$C_{21}H_{28}N_8O_6S \cdot 0.5C_3H_8O$
6	NHC_6H_4CN-*m*	B	44[d]	>140[e]	$C_{22}H_{28}N_8O_4S$
7	$NHC_6H_4CONMe_2$-*m*	B[c,h]	19[d]	>192[e]	$C_{24}H_{34}N_8O_5S \cdot 1.5H_2O$
8	NEt_2	E[i]	18[j]	189	$C_{19}H_{33}N_7O_4S$
9	c-$N(CH_2CH_2)_2O$	E[i]	39[d]	220–221	$C_{19}H_{31}N_7O_5S$

[a]Yield of analytically pure material except where indicated. [b]*Anal.* C, H, N. [c]Crude product purified by column chromatography (elution from silica gel with 9:1 Me_2CO–H_2O) prior to recrystallization. [d]Recrystallized from *i*-PrOH–H_2O. [e]Decomposed over broad range. [f]Analytical sample had mp >130 dec. [g]Product precipitated from reaction mixture by addition of MeCN and Me_2CO. [h]Product precipitated from reaction mixture by addition of MeCN. [i]MeOH used as hydrogenation solvent. [j]Recrystallized from *i*-PrOH–petroleum ether (bp 65–110°).

ticularly detrimental effect on cell membrane transport.

The two *N,N*-dialkylureido derivatives **8** and **9** were only fair reversible inhibitors of the enzyme and had no detectable effect on the L1210 cell culture. Thus the terminal *N*-phenyl group of compounds of type I is a requirement for *in vitro* activity.

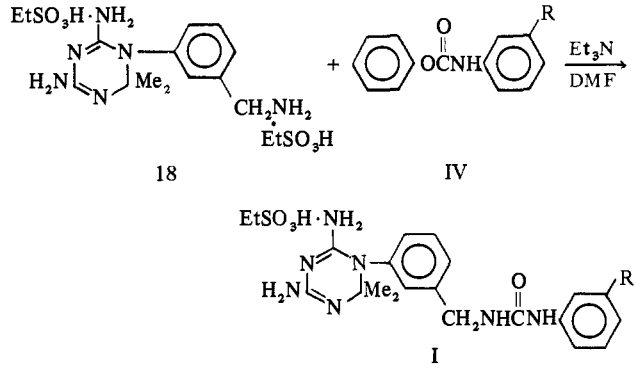
The pyrimidines (III, Table II) were also excellent inhibitors of dihydrofolate reductase. All of these compounds had ED_{50} values of <1 μM against L1210 cell culture, and three of them [*m*-Cl (**12**), *m*-NO_2 (**14**), and *m*-CN (**15**)] displayed oustanding activity. In fact, introduction of the *m*-NO_2 group on the terminal benzene ring (*cf.* **14**) increased potency by four orders of magnitude with respect to the unsubstituted compound **11**. Presumably these dramatic differences in activity are a reflection of variation in membrane transport, since all are comparable inhibitors of the enzyme. The substituent effects appear unrelated to hydrophobic-hydrophilic character. Electronic factors seem to dominate, as activity can be correlated in part with the electron-withdrawing power of the 3 substituent.

Although none of the triazines (I) surpassed the activity of **1** *in vitro*, some (**2–5**) are sufficiently active to be considered for *in vivo* screening against L1210 mouse leukemia. Since **1** may suffer from metabolic degradation of the sulfonyl fluoride group,[5,6] these analogs may be more stable *in vivo*. Also, because of our interest in antifolates suitable for intravenous administration,[1] we noted that some of the triazines (*e.g.*, **2–4**) had solubilities of ≥30 mg/ml in H_2O.

Even though the pyrimidines (III) are more distantly related to the lead compound **1**, the exceptional potency of cell culture inhibition by **12**, **14**, and **15** makes these compounds reasonable candidates for *in vivo* investigation.

Chemistry. The *N*-phenylurea moiety of I (physical properties in Table III) was introduced by reaction of **18**[7] with a phenyl *N*-phenylcarbamate (IV) in DMF in the presence of Et_3N (Scheme I). Best results were obtained

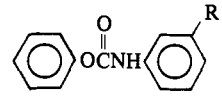
Scheme I



when the carbamate was used in 100% excess. Nevertheless, the reaction frequently proceeded in low yield, and column chromatography was sometimes required to purify the product. The carbamates (IV, Table IV) were readily obtained by treatment of the appropriate aniline with phenyl chloroformate.

The route outlined in Scheme I was unsuccessful for the preparation of the *N,N*-dialkylureido derivatives (II; physical properties in Table III), because phenyl or *p*-nitrophenyl carbamates obtained from secondary amines were found to be too unreactive, presumably due to steric hindrance. Consequently, an alternative pathway was employed

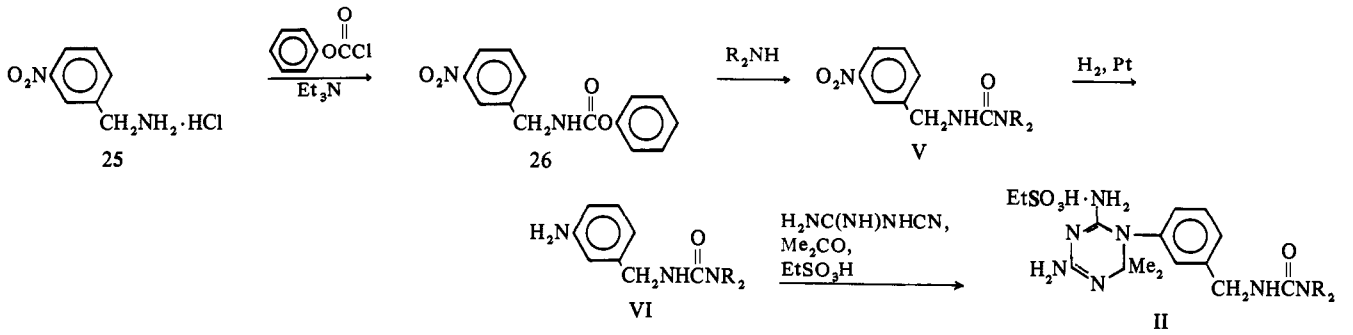
Table IV. Physical Constants of



No.	R	Yield,[a,b] %	Mp, °C	Formula[c]
19	H	87[d]	128–129[e]	
20	Cl	84[d]	84[f]	$C_{13}H_{10}ClNO_2$
21	OMe	55[d]	61–62[g]	$C_{14}H_{13}NO_3$
22	NO_2	92[d]	125–126[h]	$C_{13}H_{10}N_2O_4$
23	CN[i]	73[d,j]	108–109[f]	$C_{14}H_{10}N_2O_2$
24	$CONMe_2$[k]	59[l,m]	155–156	$C_{16}H_{16}N_2O_3$

[a]All compounds prepared by method A. [b]Yield of analytically pure material unless otherwise indicated. [c]*Anal.* C, H, N. [d]Yield of unrecrystallized product, homogeneous on tlc. [e]Lit. mp 124° [R. Leuckart, *Chem. Ber.*, 18, 873 (1885)]. [f]Analytical sample recrystallized from C_6H_6–petroleum ether (bp 65–110°) had unchanged melting point. [g]Analytical sample recrystallized from C_6H_6–petroleum ether (bp 30–60°) had mp 81–82° (possibly a different crystalline form). [h]Analytical sample recrystallized from C_6H_6–petroleum ether (bp 65–110°) had mp 126–127°. [i]Requisite amine obtained by Pd-catalyzed hydrogenation of *m*-nitrobenzonitrile. [j]Overall yield from *m*-nitrobenzonitrile. [k]Requisite amine obtained by hydrogenation of *N,N*-dimethyl-*m*-nitrobenzamide: O. L. Brady and F. H. Peakin, *J. Chem. Soc.*, 2267 (1929). [l]Overall yield from *N,N*-dimethyl-*m*-nitrobenzamide (see reference in footnote *k*). [m]Recrystallized from EtOH.

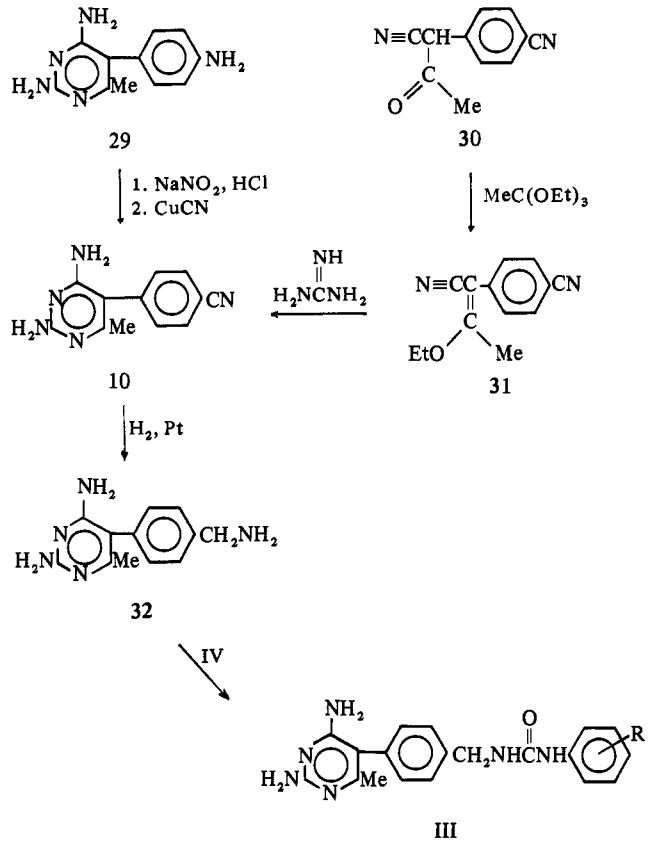
Scheme II



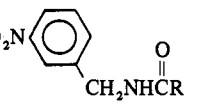
(Scheme II). Treatment of *m*-nitrobenzylamine hydrochloride (**25**)[8] with excess phenyl chloroformate in the presence of Et_3N afforded the phenyl carbamate **26** (Table V), which readily yielded a urea (V, Table V) upon reaction with a dialkylamine. The conversion of V to II *via* VI was carried out by the usual method.[9]

The pyrimidines (III, physical properties in Table VI) were prepared according to Scheme III. The cyanophenyl-

Scheme III



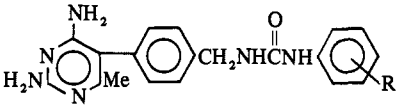
pyrimidine (**10**)[4] was synthesized by two different routes. In the first (method F), the aminophenylpyrimidine (**29**)[10] was converted *via* the Sandmeyer reaction to **10**. The alternative pathway (method G), a modification of the procedure of Julia and Chastrette,[4] involved conversion of **30**[4] to the enol ether **31** with triethyl orthoacetate followed by cyclization with guanidine. The aminomethyl derivative **32** was obtained by hydrogenation of **10** in the presence of PtO_2. Reaction of **32** with the appropriate phenyl *N*-phenylcarbamate (IV, Table IV) in DMF yielded the urea (III). In this case, unlike that of the triazines, use of a single equivalent of the carbamate was satisfactory.

Table V. Physical Constants of 

No.	R	Method	Yield,[a] %	Mp, °C	Formula[b]
26	OC_6H_5	C	59[c]	115	$C_{14}H_{12}N_2O_4$
27	NEt_2	D[d]	107[e]	Oil	
28	c-$N(CH_2CH_2)_2O$	D	66[e]	153[f]	$C_{12}H_{15}N_3O_4$

[a]Yield of analytically pure material unless otherwise indicated. [b]*Anal.* C, H, N. [c]Recrystallized from MeOH-H_2O. [d]Product extracted into EtOAc. [e]Yield of crude or unrecrystallized material, homogeneous on tlc. [f]Analytical sample recrystallized from EtOAc-petroleum ether (bp 65–110°) had unchanged melting point.

Table VI. Physical Constants of



No.	R	Yield,[a,b] %	Mp, °C	Formula[c]
11	H	42[d]	217–218	$C_{19}H_{20}N_6O$
12	3-Cl	34[e]	195–198	$C_{19}H_{19}ClN_6O$
13	3-OMe	20[e]	176–179	$C_{20}H_{22}N_6O_2$
14	3-NO_2	22[f]	212–214	$C_{19}H_{19}N_7O_3$
15	3-CN	26[e]	228–230	$C_{20}H_{19}N_7O \cdot 0.25C_2H_6O$
16	3-$CONMe_2$	43[g]	178–181	$C_{22}H_{26}N_7O_2$
17	3-Me-4-SO_2F[h]	40[i]	214–216	$C_{20}H_{21}FN_6O_3S$

[a]All compounds prepared by method H. [b]Yield of analytically pure material. [c]*Anal.* C, H, N. [d]Recrystallized from $CHCl_3$–EtOH–C_6H_6. [e]Recrystallized from EtOH–H_2O. [f]Recyrstallized from 2-methoxyethanol–H_2O. [g]Recrystallized from $CHCl_3$–petroleum ether (bp 65–110°). [h]Carbamate intermediate [B. R. Baker and G. J. Lourens, *J. Med. Chem.*, 12, 101 (1969) (paper 161)] prepared in this laboratory by G. J. Lourens. [i]Recrystallized from MeOH–H_2O.

Experimental Section

Combustion values (C, H, and N) obtained by Galbraith Laboratories, Knoxville, Tenn., were within 0.4% of the theoretical values for all analytical samples. Each compound had ir and uv spectra in accord with its assigned structure; purity was confirmed by tlc on Brinkman silica gel GF. Melting points are uncorrected and were taken in capillary tubes on a Mel-Temp block.

Phenyl *N*-(*m*-Chlorophenyl)carbamate (20). Method A. A mixture of 1.57 g (10 mmol) of phenyl chloroformate, 1.28 g (10 mmol) of *m*-chloroaniline, and 40 ml of C_6H_6 was stirred at reflux for 3.5 hr, by which time all the material had dissolved, and HCl evolution ceased. The solution was filtered and concentrated to small volume and then diluted with petroleum ether. The product which crystallized was collected and washed with petroleum ether to give 2.10 g (84%) of nearly colorless crystals, mp 84° (tlc in 1:1 EtOAc–petroleum ether). The analytical sample recrystallized from C_6H_6–petroleum ether (bp 65–110°) had unchanged melting point. *Anal.* ($C_{13}H_{10}ClNO_2$) C, H, N.

1-[*m*-(*m*-Chlorophenylureidomethyl)phenyl]-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Ethanesulfonate (3). Method B.

A solution of 466 mg (1.0 mmol) of 18,[7] 494 mg (2.0 mmol) of 20, and 111 mg (1.1 mmol) of Et_3N in 3 ml of DMF was stirred at room temperature with protection from moisture. After 24 hr the precipitated product was collected on a filter and washed with a small amount of DMF, then MeCN, and finally Me_2CO. Two recrystallizations from *i*-PrOH–H_2O afforded 234 mg (46%) of white crystals which decomposed gradually >140° (tlc in 2:1 H_2O–Me_2CO). *Anal.* ($C_{21}H_{28}ClN_7O_4S$) C, H, N.

Phenyl *N*-(*m*-Nitrobenzyl)carbamate (26). Method C. A mixture of 945 mg (5.0 mmol) of 25,[8] 3.92 g (25 mmol) of phenyl chloroformate, 1.06 g (10.5 mmol) of Et_3N, and 20 ml of C_6H_6 was stirred with protection from moisture for 2 hr in an ice bath and then at room temperature. After 22 hr, the mixture was diluted with 30 ml of Me_2CO and filtered to remove the precipitated $Et_3N \cdot HCl$ which was washed with Me_2CO. The combined filtrate and washings were spin evaporated *in vacuo*. Upon trituration of the residual oil with petroleum ether, a solid was readily obtained. The product was isolated and washed with petroleum ether. Recrystallization first from C_6H_6–petroleum either (bp 65–110°) and then from 2-methoxyethanol–H_2O gave 769 mg (59%) of colorless crystals, mp 115° (tlc in 1:1 EtOAc–petroleum ether). *Anal.* ($C_{14}H_{12}N_2O_4$) C, H, N.

***N*-(*m*-Nitrobenzylcarbamoyl)morpholine (28).** Method D. A solution of 354 mg (1.3 mmol) of 26 and 0.9 ml of morpholine in 5 ml of MeCN was stirred at room temperature with protection from moisture for 19 hr and then added to 50 ml of H_2O. Crystallization of product occurred readily. After standing in the cold, the solid was collected on a filter and washed with H_2O to give 227 mg (66%) of colorless crystals, mp 153° (tlc in EtOAc). The analytical sample recrystallized from EtOAc–petroleum ether (bp 65–110°) had unchanged melting point. *Anal.* ($C_{12}H_{15}N_3O_4$) C, H, N.

1-[*m*-(*N*,*N*-Dialkylureidomethyl)phenyl]-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Ethanesulfonates (II). Method E. The nitro intermediates V were catalytically hydrogenated and the resulting crude amines VI condensed with cyanoguanidine and Me_2CO[11] in the presence of $EtSO_3H$ as described previously.[9]

5-(*p*-Cyanophenyl)-2,4-diamino-6-methylpyrimidine (10). A. Method F. A solution of 12.9 g (60 mmol) of 29[10] in 25 ml of concentrated HCl obtained by warming the mixture on a steam bath was diluted to 50 ml with H_2O and then cooled to 0–5° in an ice bath. Next, a solution of 4.1 g (60 mmol) of $NaNO_2$ in 5 ml of H_2O was added dropwise until a positive starch-iodide test was observed. After neutralization by addition of anhydrous Na_2CO_3 at 0°, the solution of diazonium salt was added dropwise over 1 hr to a vigorously stirred CuCN solution[12] maintained at 0°. After stirring for an additional 2 hr, the mixture was allowed to warm to room temperature and then filtered. The dark brown solid obtained after washing with H_2O was dissolved in warm 2 *N* HCl, decolorized with charcoal, and filtered. Basification of the filtrate with 2 *N* NaOH gave 8.8 g (65%) of white powder, mp 350° dec (lit.[4] mp 350° dec) (tlc in 4:1 $CHCl_3$–EtOH).

B. Method G. A solution of 27.0 g (150 mmol) of 30[4] in 100 ml of triethyl orthoacetate was warmed to 70° for 2 hr and then distilled until 50 ml of low-boiling distillate had been collected. The excess triethyl orthoacetate was removed at 80° under reduced pressure to give a red oil (31) which was homogeneous by tlc ($CHCl_3$).

To 9.7 g (180 mmol) of NaOMe dissolved in 200 ml of EtOH was added 17.3 g (180 mmol) of guanidine · HCl. After stirring for 15 min, the mixture was filtered through a sintered glass funnel. The filtrate was added to the crude oil (31) prepared as above. This mixture was heated under reflux for 24 hr, then cooled to 0°, and filtered to give 18.3 g (55%) of white powder, mp 350° dec.

5-[*p*-(Aminomethyl)phenyl]-2,4-diamino-6-methylpyrimidine (32). A partial solution of 4.5 g (20 mmol) of 10 in 100 ml of 1 *N* HCl and 100 ml of EtOH was obtained by warming for 15 min. After addition of 200 mg of PtO_2, the mixture was shaken with H_2 at 2–3 atm until the required amount of H_2 had been taken up. The catalyst was removed by filtration through Celite. Neutralization of the filtrate with 2 *N* NaOH precipitated a white solid which was isolated and recrystallized from EtOH to give 3.7 g (82%) of the product: mp 289–291° (tlc in 4:1 $CHCl_3$–EtOH); λ_{max} (pH 1) 275 mμ, (pH 11) 288 mμ. *Anal.* ($C_{12}H_{15}N_5$) C, H, N.

2,4-Diamino-6-methyl-5-[*p*-(phenylureidomethyl)phenyl]pyrimidine (11). Method H. To 0.18 g (0.8 mmol) of 32 was added 0.17 g (0.8 mmol) of 19 and 10 ml of DMF. The mixture was stirred at room temperature for 24 hr with protection from moisture and then added to 30 ml of H_2O. The white precipitate was collected on a filter and washed with $CHCl_3$. Recrystallization from $CHCl_3$–EtOH–H_2O gave 0.12 g (42%) of product: mp 217–218° (tlc in 4:1 $CHCl_3$–EtOH); λ_{max} (pH 1) 272 mμ, (pH 11) 288 mμ. *Anal.* ($C_{19}H_{20}N_6O$) C, H, N.

Acknowledgments. We are indebted to Mrs. Julie Beardslee and Mrs. Pauline Minton for performing the enzyme assays and to Dr. Florence R. White of Drug Research and Development, National Cancer Institute, for supplying the L1210 cell culture data.

References

(1) B. R. Baker and W. T. Ashton, *J. Med. Chem.*, 16, 209 (1973) (paper 197).
(2) B. R. Baker, N. M. J. Vermeulen, W. T. Ashton, and A. J. Ryan, *ibid.*, 13, 1130 (1970) (paper 173).
(3) B. R. Baker and G. J. Lourens, *ibid.*, 11, 38 (1968) (paper 112).
(4) J. Julia and F. Chastrette, *Bull. Soc. Chim. Fr.*, 2247 (1962).
(5) A. J. Ryan, N. M. J. Vermeulen, and B. R. Baker, *J. Med. Chem.*, 13, 1140 (1970) (paper 174).
(6) E. Fölsch and J. R. Bertino, *Mol. Pharmacol.*, 6, 93 (1970).
(7) B. R. Baker and G. J. Lourens, *J. Med. Chem.*, 11, 26 (1968) (paper 109).
(8) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926).
(9) B. R. Baker and W. T. Ashton, *J. Med. Chem.*, 13, 1165 (1970) (paper 179).
(10) P. B. Russell and G. H. Hitchings, *J. Amer. Chem. Soc.*, 73, 3763 (1951).
(11) E. J. Modest, *J. Org. Chem.*, 21, 1 (1956).
(12) H. T. Clarke and R. R. Read, "Organic Syntheses," Collect. Vol. I, H. Gilman, Ed., Wiley, New York, N. Y., 1941, p 514.