search of the University of California, the Research Laboratories of Merck Sharp and Dohme, and the National Institutes of Health (GM 28128) for their generous support of our research. We are grateful to Dr. H. Webb for recording the mass spectral data.

Registry No. 3, 20662-84-4; **5a**, 14224-99-8; **5b**, 20662-92-4; **5c**, 23012-31-9; **6**, 76346-79-7; **7** (*E*), 76346-80-0; **7** (*Z*), 76346-81-1; **8**, 76346-82-2; **9** (isomer 1), 76346-83-3; **9** (isomer 2), 76346-84-4; **11**, 76346-85-5; 2-(β-naphthylethyl)-4,5-dimethyloxazole, 76346-86-6; 2-(3-hydroxy-3-phenylpropyl)-4,5-dimethyloxazole, 76346-87-7; 1-(2,4,5-trimethyl-2-oxazolyl)cyclohexan-1-ol, 76346-88-8; 2-ethyl-(2-hydroxyl-2-phenyl)-4,5-dimethyloxazole, 76346-89-9; 2-[2-(2-furyl)-2-hydroxylethyl]-4,5-dimethyloxazole, 76346-90-2; 1-[2-(4,5-dimethyl-2-oxazolyl)-1-hydroxylethyl]ferrocene, 76346-70-8; 2-ethyl-4,5-diphenyloxazole, 53833-30-0; 1-(2-methyl-4,5-diphenyl-2-oxazolyl)cyclopentan-1-ol, 35491-02-2; 1-(2-methyl-4,5-diphenyl-2-oxazolyl)cyclohexen-2-en-1-ol, 76346-91-3; 2-(3-butenyl)-4-methyl-5-phenyloxazole, 76346-92-4; 1-(5-phenyl-4-methyl-2-oxazolyl)octan-2-ol, 76346-93-5; 2-isobutyl-4-phenyl-5-methyloxazole, 76346-94-6; benzaldehyde, 100-52-7; cyclohexanone, 108-94-1; (chloromethyl)-benzene, 100-44-7; 2-(bromomethyl)naphthalene, 939-26-4; 2-furancarboxaldehyde, 98-01-1; formylferrocene, 12093-10-6; phenyloxirane, 96-09-3; cyclopentanone, 120-92-3; 2-cyclohexen-1-one, 930-68-7; 3-bromo-1-propene, 106-95-6; chlorotrimethylsilane, 75-77-4; heptanal, 111-71-7; 2-iodopropane, 75-30-9; iodomethane, 74-88-4; cinnamaldehyde, 14371-10-9.

Chemistry of 2-Substituted Pyrimidines. Studies Directed toward the Synthesis of the Pyrimidine Moiety of Bleomycin

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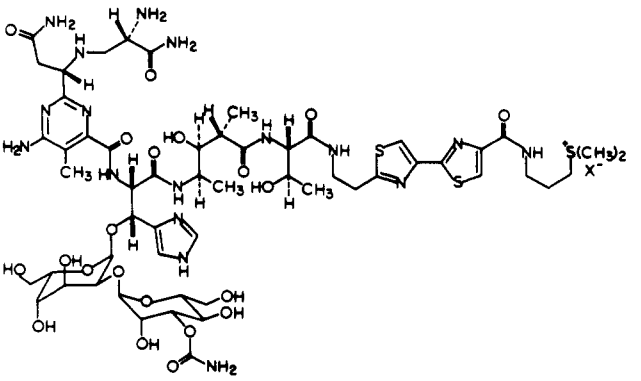
Synthetic approaches to 2-substituted pyrimidines have been studied in an effort to facilitate the preparation of the pyrimidine moiety of bleomycin (**2**). Ethyl 2,5-dimethyl-4-oxopyrimidine-6-carboxylate (**4**) has been utilized as starting material; its conversion to the respective ethyl 2-(carboalkoxy)-5-methyl-4-oxopyrimidine-6-carboxylates provided electrophilic intermediates for attempted elaboration of the 2-substituent, while treatment of **4** with pyridine promoted the nucleophilic addition of the C-2 methyl group to chloral. Introduction of the requisite β-aminoalaninamide substituent was attempted in several ways, including conjugate addition reactions, the use of imine or enamine intermediates, and via nucleophilic halide displacement. Of particular interest were the use of 4-azidopyrimidines as synthetic intermediates leading to the required 4-aminopyrimidines and the solvent-dependent rearrangement of ethyl 3-azido-3-[4-azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]propionate (**46**) to ethyl 3-amino-3-[4-azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]acrylate (**47**) at ambient temperature.

The bleomycins are a family of structurally related antitumor antibiotics elaborated by the fungus *Streptomyces verticillus*.[3] Certain of the bleomycins are of considerable interest at present because of their clinical utility in the treatment of squamous cell carcinomas and malignant lymphomas.[4] As part of an effort to effect a convergent total synthesis of bleomycin A_2 (**1**),[5] we have recently prepared the pyrimidine moiety of bleomycin (**2**) blocked in a form suitable for reconstruction of the antibiotic.[6] Presently, we describe the chemistry of some 2-substituted pyrimidines, on the basis of which we were able to devise



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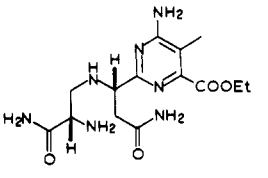
a workable synthesis of an appropriate derivative of **2**.



2

In addition to solution of the stereochemical problem, successful construction of the requisite pyrimidine involved initial synthesis of a suitable 2-alkylpyrimidine and its conversion to a (pyrimidin-2-yl)propionamide, as well as introduction of the β-aminoalaninamide substituent. Particularly challenging was introduction of the amino group at C-4 of the pyrimidine and selective manipulation

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(2) Alfred P. Sloan Fellow, 1975-1979; NIH Research Center Development Awardee, 1975-1980. Present Address: Department of Chemistry, University of Virginia, Charlottesville, VA 22901.

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(6) Arai, H.; Hagmann, W. K.; Suguna, H.; Hecht, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 6631.

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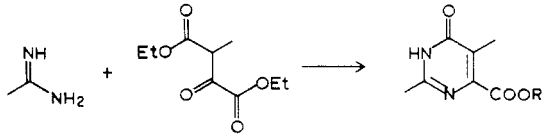
of the three carboxylates in a fashion that permitted efficient introduction of the requisite substituents and functionalities. Two facets of the synthesis were of special concern: the need to identify a (minimally) protected derivative of **2** suitable for reconstruction of bleomycin and to develop a facile, flexible route to this compound (and analogues thereof). Our studies therefore focused on the chemical characteristics of pyrimidine **2**, on intermediates with acceptable physical characteristics, and on transformations that provided such species cleanly.

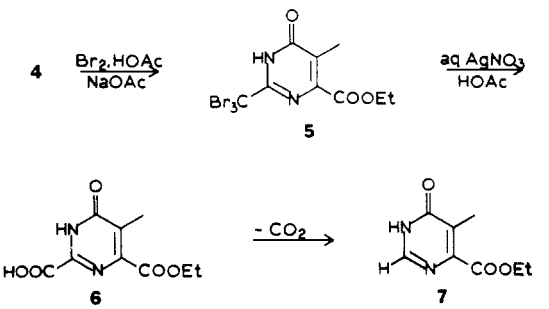
Synthesis and Chemistry of 2-Methylpyrimidine Derivatives. Appropriately substituted pyrimidine derivatives were readily accessible by conventional methods.[7] In particular, the synthesis of 2,5-dimethyl-4-oxopyrimidine-6-carboxylic acid (**3**) has been reported,[8] al-



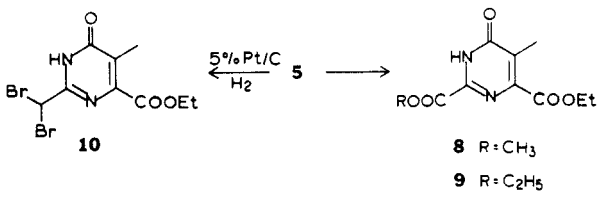
3 R = H
4 R = C_2H_5

though no experimental details were provided. When equimolar amounts of acetamidine and diethyl oxalpropionate[9] were heated at reflux in ethanolic potassium hydroxide, the cooled reaction mixture deposited potassium 2,5-dimethyl-4-oxopyrimidine-6-carboxylate in yields up to 50%. Crystallization of the product from hydrochloric acid afforded the free acid. Esterification (absolute C_2H_5OH, H_2SO_4, $SOCl_2$, reflux, 72 h) gave ethyl 2,5-dimethyl-4-oxopyrimidine-6-carboxylate (**4**) in 98% yield. It was hoped that selective oxidation of the C-2 methyl group to afford the respective carboxylate would provide a species that could subsequently be activated (e.g., as the acid chloride) and employed for the acylation of a suitable malonic acid derivative or some equivalent species. The β-keto ester so derived would represent a reasonable intermediate for the construction of derivatives of type **2**, e.g., by initial reductive amination[11] with N^{α}-(*tert*-butoxycarbonyl)-L-α,β-diaminopropionamide.[6]

Consistent with the report[12] that 2-methylpyrimidine could not be oxidized readily, treatment of **3** with ceric ammonium nitrate in acetic acid[13] afforded none of the oxidized product.[14] However, as also observed for 2-methylpyrimidine,[15] bromination of **3** and **4** proceeded readily in the presence of bromine–acetic acid–sodium acetate;[16] bromination of ester **4** provided ethyl 5-methyl-2-(tribromomethyl)-4-oxopyrimidine-6-carboxylate (**5**) as a pale yellow solid in 92% yield. Treatment of **5** with 3 equiv of $AgNO_3$ in 95% aqueous acetic acid (25 °C) effected little hydrolysis of the tribromomethyl group over a period of 48 h. Under more vigorous conditions (100 °C,



1 h) hydrolysis did occur, but the initially formed carboxylate underwent extensive decarboxylation; isolated as the major product was ethyl 5-methyl-4-oxopyrimidine-6-carboxylate (**7**). More useful was treatment of pyrimidine **5** with $AgNO_3$ in aqueous methanol which effected its conversion (90% yield) to ethyl 2-(carbomethoxy)-5-methyl-4-oxopyrimidine-6-carboxylate (**8**). Analogous transformation of **5** in ethanol afforded diethyl 5-methyl-4-pyrimidine-2,6-dicarboxylate (**9**) in 51% yield.

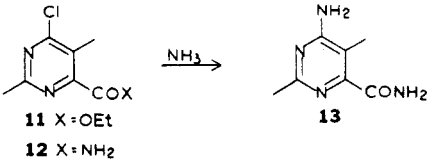


8 R = CH_3
9 R = C_2H_5

When pyrimidinecarboxylic acid **6** was treated with thionyl chloride (2 equiv, 25 °C) in an effort to obtain the respective acid chloride, a vigorous exothermic reaction ensued. The cooled reaction mixture was then treated with C_2H_5OH–$(C_2H_5)_3N$ (25 °C, 1 h) to effect conversion of the putative acid chloride to diester **9** for purposes of characterization. However, extractive workup afforded only a single product identical with decarboxylated pyrimidone **7**. Although the desired acid chloride could not be obtained conveniently, the C-2 carboxylate moieties in **8** and **9** were found to be quite electrophilic and could be utilized as synthetic equivalents of the acid chloride discussed above.

Additionally, it was found that (tribromomethyl)pyrimidine **5** underwent hydrogenolysis over 5% platinum-on-carbon, affording the respective dibromide (**10**) as a viscous oil. Compound **10** may be a suitable precursor for the pyrimidine-2-carboxaldehyde, and as such is of interest in the context of an alternate synthesis of the pyrimidine moiety of bleomycin.[17]

Introduction of the 4-Amino Group. 4-Aminopyrimidines are typically prepared by ammonolysis of the respective 4-halopyrimidines; the latter are obtained by treatment of 4-pyrimidones with $POCl_3$.[18] Initially, pyrimidone **4** was employed as a model compound. After conversion to the respective 4-chloro species (**11**), treat-



11 X = OEt
12 X = NH_2
13

ment with ethanolic ammonia afforded mainly the respective chloropyrimidine-6-carboxamide (**12**); transfor-

(7) (a) Brown, D. J. "The Pyrimidines"; Weissberger, A., Ed.; Interscience: New York, 1962; p 49. (b) Brown, D. J. "The Pyrimidines"; Weissberger, A., Taylor, E. C., Eds.; Wiley-Interscience: New York, 1970; Supplement 1, p 31.
(8) Muraoka, Y.; Takita, T.; Maeda, K.; Umezawa, H. *J. Antibiot.* **1970**, *23*, 252.
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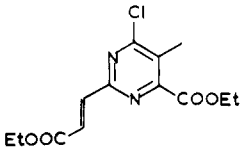
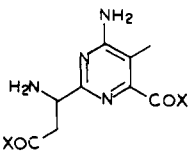
(13) Syper, L. *Tetrahedron Lett.* **1966**, 4493.
(14) Also utilized (unsuccessfully) for the oxidation were chromic acid, selenous acid, lead tetraacetate, and mercuric acetate.
(15) Holland, A.; Slack, R. *Chem. Ind. (London)* **1954**, 1203.
(16) Hammick, D. L. *J. Chem. Soc.* **1923**, *123*, 2882.
(17) Umezawa, Y.; Morishima, H.; Yoshioka, T.; Otsuka, M.; Ohno, M. "Bleomycin: Chemical, Biochemical and Biological Aspects"; Hecht, S. M., Ed.; Springer-Verlag: New York, 1979; p 63ff.
(18) Reference 7a, p 123ff.

mation to 4-aminopyrimidine **13** occurred to some extent after 7 days at 25 °C, but **13** could not be isolated in good yield.

Yoshioka et al.[19] have reported the conversion of chloropyrimidine **14** to aminopyrimidine **16** in 20% yield via



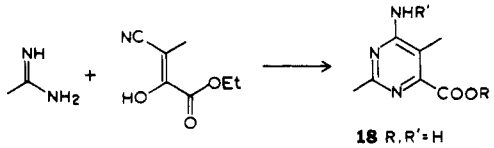
14



15 X = NH_2
16 X = OH
17 X = OMe

successive treatments with ethanolic ammonia (135 °C, 18 h) and 6 N hydrochloric acid (105 °C, 18 h). We attempted to repeat this work in an effort to define conditions under which **16** could be prepared more efficiently. Treatment of compound **14** with ethanolic ammonia at room temperature resulted primarily in formation of the corresponding C-6 carboxamide, although in some experiments introduction of the 4-amino group also occurred to a limited extent. At higher temperature (100 °C, pressure bottle, 48 h) modification of the C-2 substituent was also observed and **15** was formed with reasonable efficiency. The product was characterized after conversion to diacid **16** (and also to the respective dimethyl ester (**17**)) by comparison of physical properties with those reported[20] and by consideration of the pH dependence of the ^1H NMR chemical shifts in **16** relative to those in compounds **3** and **18**. Although the conversion **14** → **16** could be carried out in 70–75% yield on a small (<0.5 g) scale, when run on a larger scale incomplete ammonolysis of the C-2 substituent was a frequent problem.

The difficulties encountered above prompted us to consider introduction of the amino group during construction of the pyrimidine nucleus. Accordingly, acetamidine and ethyl cyanomethylpyruvate were condensed in ethanolic solution over a period of 7 days. Workup afforded the desired 4-amino-2,5-dimethylpyrimidine-6-carboxylic acid (**18**) as an off-white solid in 47% yield. After esterification of the C-6 carboxylate (CH_3OH, H_2SO_4, $SOCl_2$, reflux, 48 h) in 66% yield, acetylation proceeded readily in chloroform solution, affording methyl 4-acetamido-2,5-dimethylpyrimidine-6-carboxylate (**20**) in 57%



18 R,R' = H
19 R = Me, R' = H
20 R = Me, R' = Ac

yield from **19**. Both **18** and **20** were treated with chloral in an effort to introduce the requisite C-2 substituent (cf. Scheme I) but neither provided the desired product.

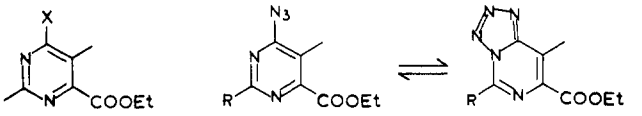
The difficulties encountered in introduction of the C-4 amino group efficiently and in a fashion consistent with the preparation of pyrimidine **2** prompted an investigation of alternate synthetic approaches. Treatment of pyrimidones **3** or **4** with phenyl phosphorodiamidate, according to the work of Rosowsky and Papathanasopoulos,[21] gave

Table I. Solvolysis of the C-2 Esters in Pyrimidone-2,6-dicarboxylates 8 and 9[a]

pyrimidone	reactants	conditions	product compn (8 or 9/product)
8	C_2H_5OH	25 °C, 23 h	100:0
8	C_2H_5OH, DMAP	25 °C, 23 h	28:72
8	CH_3OH, DMAP	25 °C, 24 h	100:0
8	DMF, H_2O, DMAP	25 °C, 120 h	100:0
8	DMF, H_2O, DMAP	50 °C, 4 h	30:70[b]
9	CH_3OH, DMAP	25 °C, 28 h	22:78
9	CH_3OH, CH_3ONa	reflux, 20 h	0:100[c]

[a] The reactions were run as indicated with initial concentrations of 8 and 9 ranging from 0.1 to 0.7 M and ~10 mol % of 4-(dimethylamino)pyridine (DMAP) relative to 8 or 9. After workup, the distribution of products was determined by ^1H NMR analysis. Total recovery of product(s) was nearly quantitative in each case. [b] The product was 6; no decarboxylation was observed. [c] The product was dimethyl 5-methyl-4-oxopyrimidine-2,6-dicarboxylate.

complex mixtures of products. However, much better results were obtained when chloropyrimidine **11** was treated with sodium azide in DMF. After extractive workup, ethyl 4-azido-2,5-dimethylpyrimidine-6-carboxylate (**21**) was obtained as colorless needles from



21 X = N_3
22 X = NH_2

i ⇌ ii

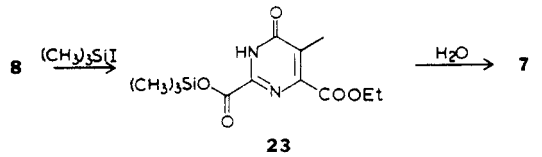
hexane (99% yield). The azidopyrimidine had two properties suggestive of the utility of intermediates of this type in the elaboration of **2**: it was freely soluble in a number of organic solvents and could be converted to the corresponding 4-aminopyrimidine (**22**) quantitatively by hydrogenolysis over 5% Pd/C. A single difficulty was noted in the manipulation of such azidopyrimidines, namely, their tendency to exist in equilibrium with the corresponding tetrazoles (i.e., i ⇌ ii). While of no consequence to the chemistry of the azidopyrimidines, this feature did serve to complicate interpretation of the spectral data corresponding to the synthetic intermediates.

Elaboration of the Pyrimidylpropionamide Moiety. (1) Via an Electrophilic C-2 Substituent. The C-2 methyl ester of pyrimidinedicarboxylate **8** was found to be surprisingly reactive. As described below, a variety of nucleophiles added rapidly to this ester without affecting the C-6 carboxylate. The additional observation that nucleophiles exhibited similar selectivity toward the C-2 ester in diethyl 5-methyl-4-oxopyrimidine-2,6-dicarboxylate (**9**) suggested that this enhanced reactivity can be attributed to the adjacent ring nitrogen atoms.

Initially, a series of solvolysis reactions was performed; the results are summarized in Table I. As shown in the table, transesterification of the C-2 ester in compounds **8** and **9** proceeded at room temperature in a transformation that depended on the presence of 4-(dimethylamino)-pyridine (DMAP). Neither compound underwent detectable transesterification at C-6. Treatment of **9** with 2 equiv of $NaOCH_3$ in CH_3OH at reflux for 20 h effected complete conversion to the C-2 methyl ester **8**, but under these conditions exchange at C-6 also proceeded to completion. Interestingly, DMAP also catalyzed the hydrolysis of **8** under conditions (50 °C, 4 h) that did not result in decarboxylation of the formed C-2 carboxylate derivative

(19) Yoshioka, T.; Muraoka, Y.; Takita, T.; Maeda, K.; Umezawa, H. *J. Antibiot.* **1972**, *25*, 625.
(20) Muraoka, Y.; Takita, T.; Maeda, K.; Umezawa, H. *J. Antibiot.* **1970**, *23*, 252.
(21) Rosowsky, A.; Papathanasopoulos, N. *J. Heterocycl. Chem.* **1972**, *9*, 1235.

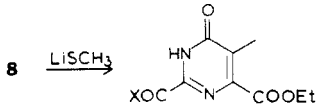
6. Diester 8 was also found to react with trimethylsilyl iodide;[22] after 120 h at 35 °C, the reaction mixture contained methyl iodide (~90% of theoretical) and compound 8 (~10%), as well as a silylated product. Structure **23** is



23

assigned to this compound on the basis of spectral data and the observation that removal of the solvent and all volatile components from the reaction mixture, followed by treatment with water, gave ethyl 5-methyl-4-oxopyrimidine-6-carboxylate (**7**).

Several reagents have been employed for the demethylation of phenolic ethers, quaternary amines, and hindered esters;[23] certain intensely nucleophilic lithium alkylmercaptides have been particularly useful for this type of transformation.[23-25] Treatment of pyrimidine 8 with lithium methylmercaptide (DMF, 100 °C, 20 h) did afford ethyl 2-carboxy-5-methyl-4-oxopyrimidine-6-carboxylate as the lithium salt (**24**), but only in 17% yield. Also ob-



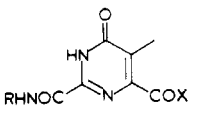
24 X = $-O^-Li^+$

25 X = SMe

tained (in 53% yield) was thioester **25**, reflecting the substantial electrophilic character of the C-2 carboxylate moiety in 8. Treatment of 8 with *p*-tolylmercaptide under the same conditions resulted in formation of the analogous products, although **24** was obtained in somewhat better (43%) yield.

The experiments outlined above suggested that esters **8** and **9** would suffice as synthetic equivalents of an acid chloride. Although the use of these species for introduction of the C-2 substituent (e.g., by the use of the dilithium salt of ethyl malonate) did not prove possible, additional model studies involving compound 8 and several amines suggested a possible alternative.

Unhindered amines, such as ammonia and benzylamine, were found to react with pyrimidine 8 at room temperature in methanolic solution, affording the expected C-2 amides (**26** and **27**, respectively) in good yields. Variable results



26 R = H, X = OEt

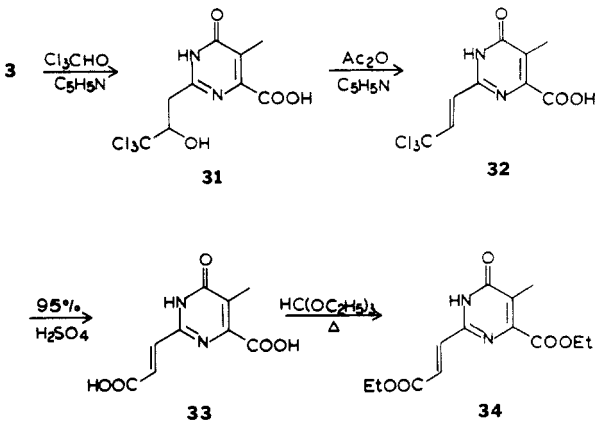
27 R = $C_6H_5CH_2$, X = OEt

28 R = Me_2, X = Me_2N

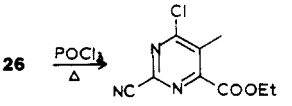
29 R = $-(CH_2)_4-$, X = OEt

were obtained with more hindered amines. When dissolved in a solution of 25% aqueous dimethylamine (25 °C, 36 h), pyrimidine 8 underwent amide exchange at both C-2 and C-6, affording **28** in quantitative yield. In comparison, when a methanolic solution of 8 was stirred in the presence of 4.5 equiv of diethylamine or morpholine (25 °C, 20 h), no reaction took place; at higher temperature (50 °C, 2–4 h) only ester exchange was observed. These findings suggested the possible importance of steric factors in amide formation. Consistent with this interpretation, it was found that when a methanolic solution of 8 was heated in the presence of 4.5 equiv of pyrrolidine, the desired C-2 amide (**29**) formed in 23% yield. When the experiment was repeated in *tert*-butyl alcohol (reflux, 4 h), amide **29** could be isolated as a white solid in 70% yield.

Scheme I



When ethyl 2-carboxamido-5-methyl-4-oxopyrimidine-6-carboxylate (**26**) was heated in $POCl_3$, dehydration occurred, and ethyl 4-chloro-2-cyano-5-methylpyrimidine-6-carboxylate (**30**) was isolated in quantitative yield after



30

extractive workup. Analogous transformation of mono- or disubstituted amides (e.g., **27** and **28**) might be expected to result in the formation of imino chlorides and chloroimmonium chlorides, respectively. These species could then be employed in Vilsmeier-type reactions for construction of the requisite C-2 substituent.

Pyrimidine carboxamides **27** and **29** were therefore treated with $POCl_3$, $COCl_2$, and $SOCl_2$ under a variety of conditions in an effort to generate a suitable electrophile. Analysis of the reaction mixtures was carried out after workup (involving simple evaporation of the volatile components) or else subsequent to reaction of the putative activated species with one of several nucleophiles which included methanol, H_2S, dilithium ethyl malonate, and the anion derived from Meldrum's acid.[10] Treatment with each of the acid chlorides effected conversion of **27** and **29** to the respective 4-chloro species. Occasionally, modification of the C-2 substituent was observed, and additional treatment with a nucleophile provided one or more new products. However, none of these transformations proceeded cleanly or to provide material easily identifiable as the desired product. Therefore, we focused our attention on a more successful approach to the desired pyrimidylpropionamide which involved the use of the C-2 methyl group of **3** as a nucleophile.

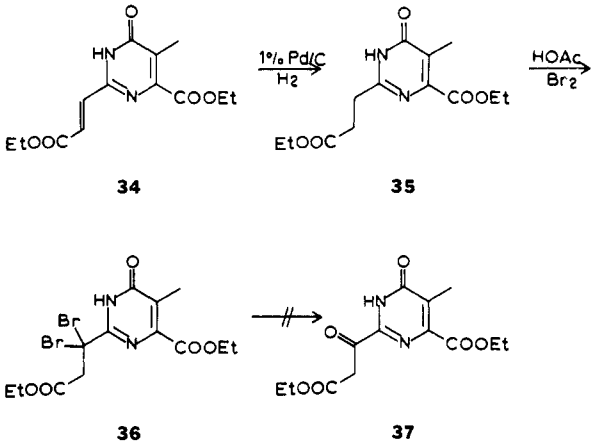
(2) Via a Nucleophilic C-2 Substituent. The two-carbon homologation of pyrimidine **3** to a 3-(pyrimidin-2-yl)acrylate derivative (**34**) has been outlined[19] but without a description of the experimental procedures employed (Scheme I). As shown in Scheme I, treatment of

(22) Ho, T. L.; Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 774.
(23) Hecht, S. M.; Kozarich, J. W. *J. Chem. Soc., Chem. Commun.* **1973**, 387.
(24) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459.
(25) Kelly, T. R.; Dali, H. M.; Tsang, W. G. *Tetrahedron Lett.* **1977**, 3859.

3 with chloral in anhydrous pyridine afforded 2-(2-hydroxy-3,3,3-trichloropropyl)-5-methyl-4-oxopyrimidine-6-carboxylic acid (31) in 67% yield, isolated as colorless needles by crystallization from ethyl acetate. Dehydration of 31 (pyridine–CH_3COOH) provided 5-methyl-2-(3,3,3-trichloro-*trans*-1-propenyl)-4-oxopyrimidine-6-carboxylic acid (32) as light yellow crystals in 85% yield. In practice, it proved to be more convenient to proceed directly from 3 to 32 without purification of the intermediate chloral adduct; the overall yield was also improved by this procedure. Subsequent hydrolysis of 32 (concentrated H_2SO_4, 70 °C, 18 h) gave 3-(6-carboxy-5-methyl-4-oxopyrimidin-2-yl)acrylic acid (33). The esterification of 33 with HCl-saturated C_2H_5OH has been reported[19] to afford diethyl ester 34 as a gummy solid in 86% yield. Although it proved difficult to repeat this transformation, clean conversion to 34 was achieved by heating diacid 33 in triethyl orthoformate for several hours. Diester 34 was obtained in 92% yield and could be crystallized from methanol as colorless needles, mp 139–141 °C.

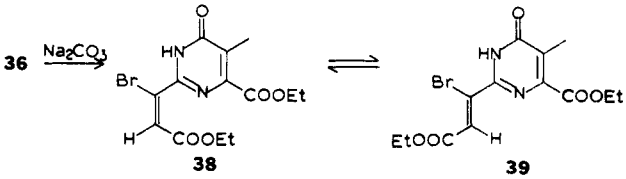
Introduction of the β-Aminoalaninamide Substituent. (1) By Conjugate Addition. Takita et al.[19,26] have reported the successful conjugate addition of the aliphatic amino group in "compound II" (16) to *N*-acetyldehydroalanine methyl ester. Although a mixture of four products was obtained, the *S,S* (and *R,R*) isomers were formed predominantly and could be separated from the diastereomers chromatographically.[27] Since it has also been reported[17] that the conjugate addition of methyl 3-amino-3-phenylpropionate to *N*-(carbobenzyloxy)-dehydroalanine methyl ester proceeded in moderate yield, it seemed of interest to utilize this procedure for introduction of the β-aminoalaninamide substituent. Accordingly, several serine derivatives were prepared for condensation with pyrimidine 17 including *N*-(carbobenzyloxy)dehydroalanine methyl ester and both the methyl ester and carboxamide derivatives of *N*-(carbobenzyloxy)-*O*-*p*-toluenesulfonylalanine. Unfortunately, all of these compounds were found to react sluggishly with 17, and this approach was abandoned. An obvious alternative involved the conjugate addition of a suitable β-aminoalanine derivative to pyrimidine acrylate 34; this route also had the advantage of providing potential stereochemical control. Although the conversion 16 → 17 represented a simple example of the type of transformation of interest, it was found that derivatives of β-aminoalanine were not sufficiently reactive to undergo conjugate addition to 34 under reasonable conditions. In fact, even the reaction of pyrimidine 34 with benzylamine did not proceed with facility.

(2) Via Imine or Enamine Formation. Although not readily accessible by the route initially envisioned, β-keto derivatives of pyrimidinylpropionates (e.g., 37) represent versatile intermediates for the construction of pyrimidines of type 2. The successful halogenation of pyrimidine 4 and metal-assisted hydrolysis of the derived (tribromomethyl)pyrimidine (5) suggested a possible route to the intermediates of interest. Accordingly, ethyl *trans*-3-[6-(carboethoxy)-5-methyl-4-oxopyrimidin-2-yl]acrylate (34) was converted to the corresponding propionate (35) by hydrogenation over 1% palladium-on-carbon (C_2H_5OH–ethyl acetate, 3 atm of H_2, 12 h). The product, obtained as colorless microcrystals (ethanol) in quantitative yield, was stirred in acetic acid containing bromine and sodium acetate (25 °C, 40 h). Extractive workup afforded the



desired dibromide (36) as a white solid in 93% yield. Although the formation of 36 from 35 proceeded readily in analogy with the conversion 4 → 5, attempted hydrolysis of the dibromide to the respective ketone (under conditions known to hydrolyze 5) resulted only in recovery of starting material. Attempted Ag^+-assisted alcoholysis of the dibromide with ethanol and ethylene glycol (cf. 5 → 8, 5 → 9) afforded only starting material rather than the desired ketals. When more vigorous conditions were employed, attempted hydrolyses of 36 resulted either in recovery of starting material (90% H_2SO_4, 80 °C) or in complete decomposition (concentrated H_2SO_4, 100 °C).

On the assumption that the lack of reactivity of 36 could be attributed to an electron-withdrawing effect of the attached ethyl carboxylate, which might tend to suppress the development of positive character at the carbon bearing bromine, the dibromide was treated with ethanolic sodium carbonate, which effected the elimination of elements of hydrogen bromide in essentially quantitative yield. Analysis of the product by ^1H NMR indicated that it was a 7:1 mixture of vinyl bromides 38 and 39; the major



product (38) was isolated by preparative TLC (silica gel, development with 10:1 $CHCl_3$–CH_3OH) and crystallization from ethyl acetate–hexane; mp 102.5–104.5 °C.[28] Vinyl bromide 38 was then treated with 90% H_2SO_4 in an effort to effect its protonation and subsequent solvolysis to 37. The reaction mixture was poured onto ice and extracted exhaustively with ethyl acetate; the organic extract was concentrated to afford a residue (78% material balance) that was analyzed by ^1H NMR. The NMR spectrum indicated that none of the desired product was present but that isomerization of 38 had taken place to afford a 1:7 mixture of 38/39. This experiment suggested that protonation of 38 had occurred but was not accompanied by solvolysis to afford keto ester 37. In an effort to facilitate

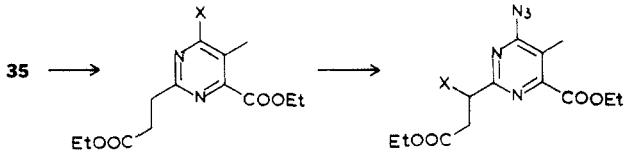
(26) Takita, T.; Muraoka, Y.; Maeda, K.; Umezawa, H. "Proceedings of the 8th Symposium on Peptide Chemistry"; Osaka, 1970; p 179.
(27) Hecht, S. M. "Bleomycin: Chemical, Biochemical and Biological Aspects", Hecht, S. M., Ed.; Springer-Verlag: New York, 1979; p 1ff.

(28) The assignment of configuration was made by comparison of the chemical shifts of the vinyl protons in 38 (δ 6.90) and 39 (δ 7.90) with those in (*E*)- and (*Z*)-ethyl 3-bromocinnamic acids (δ 6.43 and 6.96, respectively) (Williams, D.; Fleming, I. "Spectroscopic Methods in Organic Chemistry", 2nd ed.; McGraw-Hill: London, 1973). The absolute difference in chemical shifts for the pyrimidine derivatives in comparison with the cinnamates is explicable in terms of the nitrogen atoms in the pyrimidine (e.g., the corresponding vinyl protons in 2-vinylpyridine and vinylbenzene resonate at δ 6.22 and 5.59, respectively: Simons, W. W.; Zanger, M. "Sadtler Guide to NMR Spectra"; Sadtler Research Laboratories: Philadelphia, 1972).

solvolysis, **38** was treated with 1 equiv of $AgNO_3$ in 80% acetic acid (90 °C, 30 min), but none of the desired product was obtained.

Although hydrolysis of **38** (or **39**) proved not to be possible, it was thought that treatment of the bromide with an alkylamine might provide an enamine directly, the latter of which could provide a route to species of type **2**. Therefore, several attempts were made to effect a transformation of this type, but **38** failed to react with *n*-pentylamine, pyrrole, benzylamine, or ammonia under a variety of conditions. The bromide was also refractory to treatment with *n*-propylmercaptan–pyridine and sodium azide, so that other intermediates of potential interest for the preparation of **2** were also inaccessible from **38**. However, in a parallel study described below, azidopyrimidine **47** was obtained by spontaneous rearrangement of an unstable diazidopyrimidine. Successful enamine exchange[29] of **47** would also provide the desired type of intermediate leading to **2**. Therefore, azidopyrimidine **47** was heated in alcoholic solutions in the presence of methylamine and *n*-butylamine, but neither effected the requisite exchange.

(3) By Nucleophilic Halide Displacement. In spite of the lack of reactivity of dibromopyrimidine **36** in acid and its tendency to undergo facile base-promoted elimination, preliminary studies indicated that the respective monobromopyrimidine might be expected to undergo displacement, rather than elimination, in the presence of certain nucleophiles. Therefore, pyrimidine **42** was prepared for study. This material was obtained from **35**, which was first converted to the respective 4-chloropyrimidine (**40**) ($POCl_3$, reflux, 30 min). Compound **40** was

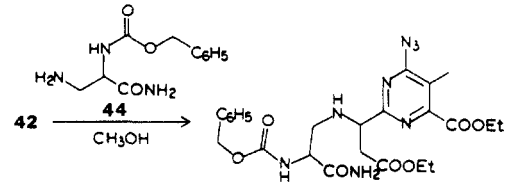


40 X=Cl
41 X=N_3
42 X=Br
43 X=$NHCH_2C_6H_5$

isolated as a viscous yellow oil (93% yield) and converted to azidopyrimidine **41** in 85–90% yield. Transformation to the desired product was then accomplished by heating **41** (CCl_4, reflux, 1 h) in the presence of 1 equiv of dioxane dibromide. Bromopyrimidine **42** was isolated (quantitative yield) as a viscous oil; the NMR and IR spectra indicated that this species existed as an equilibrium mixture of azide and tetrazole.

Conversion of key intermediate **42** to pyrimidines of type **2** would require introduction of a β-aminoalaninamide substituent at C-3 of the propionamide. Therefore, the reactivity of **42** toward several nitrogen nucleophiles was studied. Treatment of **42** with ammonia in THF (0 °C, 5 min) resulted almost exclusively in elimination of elements of HBr; neither was the desired displacement product obtained when **42** was treated with 1.5 equiv of potassium phthalimide in DMF. On the other hand, treatment of the bromopyrimidine with benzylamine in methanol (1 equiv of $NaHCO_3$, 25 °C, 2 h) afforded pyrimidine **43** in 41% yield.

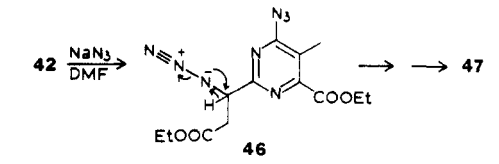
D,L-N^{α}-(Carbobenzyloxy)-β-aminoalaninamide (**44**), prepared by ammonolysis of the methyl ester of N^{α}-(carbobenzyloxy)-β-chloroalanine,[30] was dissolved in methanol and stirred in the presence of pyrimidine **42** and $NaHCO_3$



45

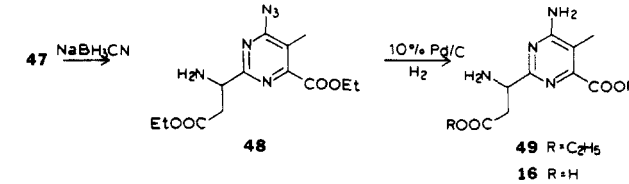
(25 °C, 12 h). After an extractive workup, the mixture of products was separated by preparative TLC. By this procedure pyrimidine **45** was formed as the major reaction product and could be separated (isolated yields up to 30%) from the accompanying elimination product. Modification of this approach to permit selective manipulation of the carboxylate moieties in the fully substituted pyrimidine, as well as (partial) control of stereochemistry, provided access to the desired pyrimidines of type **2**.[6]

Rearrangement of a Pyrimidinylalkyl Azide. One of the nucleophiles employed during the study of pyrimidine **42** was sodium azide. Reaction in CH_3OH (50 °C, 6 h) afforded several products, from which two were isolated as a mixture by preparative TLC (total yield ~40%). The (1:1) mixture consisted of the expected diazidopyrimidine (**46**) and enamine **47** whose formation can be envisioned from **46** via a Schmidt rearrangement. Remarkably, when the reaction was run in DMF (25 °C, 18 h), pyrimidine **46** was not present in significant amounts in the product mixture, but **47** could be isolated as a pale yellow solid in 79% yield. The rearrangement of alkyl azides to form imines is not an unusual reaction,[31] but the elimination of nitrogen and alkyl migration generally requires heating or strongly acidic conditions. The formation of **47** was singular in that diazidopyrimidine **46** spontaneously rearranged with exclusive hydrogen migration; neither high temperature nor strong acid was necessary. The facility of the transformation was due in no small measure to the adjacent pyrimidine moiety, as may be judged from the observed stability of ethyl 3-phenyl-3-azidopropionate in DMF at temperatures up to 100 °C.



46

As noted above, **47** could not be utilized for direct introduction of the β-aminoalaninamide substituent by enamine exchange. Nonetheless, it was of interest to attempt its conversion to "compound II" (**16**).[19,20] Therefore, pyrimidine **47** was treated with sodium cyanoborohydride (CH_3OH, pH ~3, 25 °C, 1 h); the resulting ethyl 3-amino-2-[4-azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]propionate (**48**) was isolated in 80% yield as a pale yellow oil. Catalytic hydrogenation of **51** over 10% palladium-on-carbon afforded the desired 4-aminopyrimidine (**49**) as a yellow oil, but only in low yield. Hydrolysis then



48
49 R=C_2H_5
16 R=H

(29) Becker, H. G. O. *J. Prakt. Chem.* **1961**, *12*, 294; *Chem. Abstr.* **1961**, *55*, 27299i.
(30) Wilchek, M.; Zioudrou, C.; Patchornik, A. *J. Org. Chem.* **1966**, *31*, 2865.
(31) March, J. "Advanced Organic Chemistry"; McGraw-Hill: New York, 1977; pp 1006–1008.

provided material identical with authentic 16.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover capillary tube melting point apparatus and are uncorrected. Microanalyses were performed by Chemalytics, Inc. NMR spectra were obtained on a Varian T-60 or Perkin-Elmer R-22 spectrometer; UV spectra were measured on a Cary 15 recording spectrophotometer. Mass spectra were measured on Hitachi RMU-6 and Varian MAT-44 spectrometers. A Perkin-Elmer 257 grating infrared spectrophotometer was used to record the IR spectra.

2,5-Dimethyl-4-oxopyrimidine-6-carboxylic Acid (3). To a stirred solution of acetamidine hydrochloride (15.0 g, 0.159 mol) in ethanol (125 mL) was added a solution containing 10.5 g (0.159 mol) of potassium hydroxide in 70 mL of ethanol. Potassium chloride was filtered, and the filtrate was added dropwise to ethyl ethoxalylpropionate (32.1 g, 0.159 mol). The red solution was heated at reflux overnight, treated with a second equivalent of ethanolic potassium hydroxide, and heated at reflux until a precipitate formed. The cooled solution was filtered, affording potassium 2,5-dimethyl-4-pyrimidine-6-carboxylate as a yellow solid: yield 14.0 g (43%); mp 300 °C; λ_{max} (pH 1) 260 nm, 235; λ_{max} (pH 7) 270, 226; λ_{max} (pH 12) 270, 225; NMR (D_2O, external $(CH_3)_4Si$) δ 2.05 (s, 3 H), 2.45 (s, 3 H). The sample was dissolved in 40 mL of hot water and treated with 6.3 mL of concentrated hydrochloric acid. The cooled solution was filtered and dried, affording 2,5-dimethyl-4-oxopyrimidine-6-carboxylic acid (3) as colorless plates: yield 7.41 g (65%); mp 260–261 °C; λ_{max} (C_2H_5OH, pH 1) 273 nm (ϵ 5300), 232 (7600); λ_{max} (C_2H_5OH, pH 7) 284 (5600), 224 (6300); λ_{max} (C_2H_5OH, pH 10) 273 (5400), 232 (9100); IR (KBr) 3110, 3070, 2920, 2600, 1930, 1690, 1595, 1450, 1370, 1290, 1140 cm^{-1}; NMR (Me_2SO-d_6, D_2O, $(CH_3)_4Si$) δ 2.0 (s, 3 H), 2.15 (s, 3 H); mass spectrum, m/e 168 (M^+), 150, 124, 94, 55, 44, 42.

Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80. Found: C, 49.85; H, 4.98.

Ethyl 2,5-Dimethyl-4-oxopyrimidine-6-carboxylate (4). A solution of pyrimidine 3 (25.0 g, 0.149 mol) in 1.3 L of absolute ethanol containing 20 mL of concentrated H_2SO_4 and 20 mL of $SOCl_2$ was heated at reflux for 40 h. The cooled solution was treated with an additional 20 mL of $SOCl_2$ and heated at reflux for an additional 32 h. The cooled solution was then neutralized with solid sodium bicarbonate and concentrated in vacuo. The residue was dissolved in 500 mL of chloroform and then washed with 75 mL of water. The dried ($MgSO_4$) chloroform solution was concentrated under diminished pressure, and the solid ethyl 2,5-dimethyl-4-oxopyrimidine-6-carboxylate (3) was crystallized from ethyl acetate (colorless microcrystals) in three crops: yield 28.7 g (98%); mp 171–172 °C; λ_{max} (pH 1) 274 nm, 228; λ_{max} (pH 7) 282, 222; λ_{max} (pH 10) 278; IR ($CHCl_3$) 2940, 2860, 2790, 1730, 1660, 1380, 1310, 1250, 1080 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.40 (t, 3 H, J = 7.0 Hz), 2.20 (s, 3 H), 2.52 (s, 3 H), 4.40 (q, 2 H, J = 7.0 Hz).

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17. Found: C, 55.29; H, 6.22.

Ethyl 5-Methyl-2-(tribromomethyl)-4-oxopyrimidine-6-carboxylate (5). A solution of 30.0 g (0.153 mol) of pyrimidine 4 and 125 g (0.92 mol) of sodium acetate in 450 mL of glacial acetic acid was heated at reflux. To this solution was added slowly a solution of 24 mL of bromine (75 g, 0.469 mol) in 10 mL of acetic acid. The combined solution was heated at reflux for 15 min, and the solvent and excess bromine were then removed under diminished pressure. The residue was partitioned between 400 mL of ethyl acetate and 200 mL of water, and the aqueous layer was further extracted with two 50-mL portions of ethyl acetate. The combined organic extract was dried ($MgSO_4$) and concentrated under diminished pressure, and the residue was dissolved in hot ethyl acetate, which deposited ethyl 5-methyl-2-(tribromomethyl)-4-oxopyrimidine-6-carboxylate (5) as a yellow solid upon cooling: yield 61.0 g (92%); mp 155 °C; λ_{max} (pH 1) 280 nm, 229; λ_{max} (pH 7) 282, 225; λ_{max} (pH 10) 279, 229 (sh); NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.42 (t, 3 H, J = 7.0 Hz), 2.33 (s, 3 H), 4.41 (q, 2 H, J = 7.0 Hz), 16.13 (br s, 1 H, exchanged with D_2O).

Hydrolysis of 5 with Aqueous Acetic Acid–Silver Nitrate. To a stirred solution of 1.43 g (3.30 mmol) of ethyl 5-methyl-2-(tribromomethyl)-4-oxopyrimidine-6-carboxylate in 10 mL of glacial acetic acid was added 5 mL of 2.0 M aqueous silver nitrate. The reaction mixture was heated at 100 °C in the dark for 1 h, the cooled suspension was treated with 1 mL of 5 M hydrochloric acid and then filtered, and the solid was washed with methanol. The filtrate was concentrated under diminished pressure, and the residue was dissolved in methanol, which gave ethyl 2-carboxy-5-methyl-4-oxopyrimidine-6-carboxylate (6) as an off-white solid upon cooling: yield 36 mg (5%); mp 223–225 °C dec; IR (KBr) 3500–2700 (br) and 1700–1615 (br) cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.42 (t, 3 H, J = 7.0 Hz), 2.35 (s, 3 H), 4.43 (q, 2 H, J = 7.0 Hz); mass spectrum, m/e 182, 154, 136, 108, 53; silica gel TLC (10:1 $CHCl_3$–CH_3OH) R_f 0.02.

The mother liquors were concentrated under diminished pressure, and the residue was dissolved in ethyl acetate and treated with ether, which resulted in the deposition of a small quantity of ethyl 5-methyl-4-oxopyrimidine-6-carboxylate (7) as colorless microcrystals: mp 160–162 °C; λ_{max} (C_2H_5OH) 284, 227 nm; IR (Nujol) 1724, 1680, 1658, 1607 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.42 (t, 3 H, J = 7.0 Hz), 2.39 (s, 3 H), 4.36 (q, 2 H, J = 7.0 Hz), 8.10 (s, 1 H); mass spectrum, m/e 182 (M^+), 153, 136, 108, 82, 66, 53; silica gel TLC (10:1 $CHCl_3$–CH_3OH) R_f 0.49.

Ethyl 2-(Carbomethoxy)-5-methyl-4-oxopyrimidine-6-carboxylate (8). To a stirred solution of pyrimidine 5 (2.21 g, 5.10 mmol) in 15 mL of methanol and 5 mL of ethyl acetate was added 8 mL of 2.0 M aqueous silver nitrate. The reaction mixture was stirred in the dark for 24 h, treated with 2 mL of saturated sodium chloride, and stirred for an additional 10 min. The precipitated silver salts were filtered and washed with 30 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic extract was washed successively with water (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and concentrated under diminished pressure. Crystallization from ethyl acetate afforded ethyl 2-(carbomethoxy)-5-methyl-4-oxopyrimidine-6-carboxylate as colorless microcrystals: yield 1.12 g (90%); mp 154–155 °C; IR (Nujol) 1742, 1652, 1607 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.42 (t, 3 H, J = 7.0 Hz), 2.37 (s, 3 H), 4.06 (s, 3 H), 4.44 (q, 2 H, J = 7.0 Hz); mass spectrum, m/e 240 (M^+), 195, 194, 166; silica gel TLC (10:1 $CHCl_3$–CH_3OH) R_f 0.29.

Diethyl 5-Methyl-4-oxopyrimidine-2,6-dicarboxylate. This was prepared from 1.02 g (2.36 mmol) of 5 in analogy with the preparation of 8. The desired diester was obtained as off-white microcrystals from ethyl acetate–ether: yield 307 mg (51%); mp 120–122 °C; IR (KBr) 3405, 1717, 1650–1630, 1600, 1475 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.41 (t, 3 H, J = 7.0 Hz), 1.45 (t, 3 H, J = 7.0 Hz), 2.34 (s, 3 H), 4.40 (q, 2 H, J = 7.0 Hz), 4.52 (q, 2 H, J = 7.0 Hz); mass spectrum, m/e 254, 226, 208, 180, 152, 124, 96, 82, 53.

Ethyl 2-(Dibromomethyl)-5-methyl-4-oxopyrimidine-6-carboxylate (10). A solution of 108 mg (0.25 mmol) of (tribromomethyl)pyrimidine 5 in 10 mL of ethyl acetate was hydrogenated at room temperature over 10 mg of 5% platinum-on-charcoal at 30 psi of H_2. After 20 h of reaction, the catalyst was filtered through a Celite pad, and the filtrate was concentrated. The residue was purified by preparative silica gel TLC by development with 3:7 ethyl acetate–hexane to afford recovered 5 (40 mg) and ethyl 2-(dibromomethyl)-5-methyl-4-oxopyrimidine-6-carboxylate as a viscous oil that subsequently solidified: yield 40 mg (55%; 77% based on consumed starting material); IR (film) 1722, 1665, 1602, 1560 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (t, 3 H, J = 7.0 Hz), 2.33 (s, 3 H), 4.48 (q, 2 H, J = 7.0 Hz), 6.66 (s, 1 H).

Ethyl 4-Chloro-2,5-dimethylpyrimidine-6-carboxylate (11). A suspension of 500 mg (2.38 mmol) of ethyl 2,5-dimethyl-4-oxopyrimidine-6-carboxylate (4) in 50 mL of $POCl_3$ was stirred and heated at reflux for 30 min, during which time the solid dissolved and the solution turned yellow. The solution was concentrated under diminished pressure, and the residue was treated with ice and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and concentrated, giving ethyl 4-chloro-2,5-dimethylpyrimidine-6-carboxylate as a yellow oil: yield 450 mg (83%); NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.45 (t, 3 H), 2.45 (s, 3 H), 2.75 (s, 3 H), 4.50 (q, 2 H); silica gel TLC ($CHCl_3$) R_f 0.55.

4-Chloro-2,5-dimethylpyrimidine-6-carboxamide (12). Chloro ester 11 (450 mg, 1.98 mmol) was dissolved in ethanol, and the solution was saturated with gaseous NH_3. After 24 h at room

temperature (pressure bottle), the solution was concentrated under diminished pressure, affording 4-chloro-2,5-dimethylpyrimidine-6-carboxamide in quantitative yield: IR (KBr) 3440, 3260, 3180, 1700, 1550, 1395 cm^{-1}; NMR ($CDCl_3$, Me_2SO-d_6, $(CH_3)_4Si$) δ 2.60 (s, 3 H), 2.62 (s, 3 H), 7.7 (m, 2 H); silica gel TLC (ethyl acetate) R_f 0.56.

Ethyl 3-[6-(Carboethoxy)-4-chloro-5-methylpyrimidin-2-yl]acrylate (14). A mixture of 900 mg (3.2 mmol) of ethyl 3-[6-(carboethoxy)-5-methyl-4-oxopyrimidin-2-yl]acrylate (**34**) and 20 mL of $POCl_3$ was heated at reflux for 30 min. The cooled reaction mixture was concentrated under diminished pressure, and the residue was treated with ice–water and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and concentrated, and the dark-colored residue was triturated with hexane. The hexane-soluble extract was concentrated to afford chloride **14** as a yellow oil: yield 900 mg (89%); NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.43 (m, 6 H), 2.53 (s, 3 H), 4.40 (m, 4 H), 7.40 (AB pattern, J = 15 Hz, 2 H); silica gel TLC ($CHCl_3$) R_f 0.7.

3-Amino-3-(4-amino-6-carboxy-5-methylpyrimidin-2-yl)-propionic Acid (16). A solution of 400 mg (1.27 mmol) of chloropyrimidine **14** in 30 mL of ethanol was placed in a pressure bottle and saturated with ammonia at −78 °C. The bottle was sealed and heated at 100 °C (oil bath) for 48 h. The cooled reaction mixture was concentrated under diminished pressure, affording 3-amino-3-(4-amino-6-carboxamido-5-methylpyrimidin-2-yl)propionamide (**15**) as an off-white solid that was used directly in the next reaction.

The solid obtained after ammonolysis was dissolved in 40 mL of 6 N HCl. The solution was stirred and heated at 105 °C for 18 h, cooled, and concentrated to dryness under diminished pressure (decolorization) to give an off-white solid. This solid was applied to a column of Dowex 50W resin (H^+ form); elution was with water and then with 5% NH_4OH solution. The basic eluate was concentrated to afford 220 mg (72%) of compound **16**·2HCl as a hygroscopic white solid: mp 100–101 °C dec; λ_{max} (C_2H_5OH, pH 1) 293 nm, 238; λ_{min} 266, 225; λ_{max} (C_2H_5OH, pH 7) 276, 232; λ_{min} 256, 218; λ_{max} (C_2H_5OH, pH 10) 273, 233; λ_{min} 253, 220; NMR (D_2O) δ 2.03 (s, 3 H), 2.80 (m, 2 H), 4.43 (m, 1 H); cellulose TLC (15:10:3:12 n-C_3H_7OH–pyridine–CH_3COOH–H_2O) R_f 0.18, 0.26 (lit.[20] R_f 0.146, 0.250).

Compound **16** could be converted to the respective dimethyl ester (**17**) by treatment with H_2SO_4 and $SOCl_2$ in methanol (reflux, 12 h). The oily ester was isolated by extractive workup: IR (neat) 3440, 3359, 3190, 2950, 1730, 1630, 1570, 1450, 1370, 1230, 1070, 870, 790 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.16 (s, 3 H), 2.87 (m, 3 H), 3.67 (s, 3 H), 3.93 (s, 3 H), 4.30 (t, 1 H), 6.18 (br m, 1 H); mass spectrum, m/e 268 (M^+), 252, 210.

Methyl 4-Amino-2,5-dimethylpyrimidine-6-carboxylate (19). A solution of 3.8 g (22.8 mmol) of 4-amino-2,5-dimethylpyrimidine-6-carboxylate (**18**) in 200 mL of methanol containing 5 mL of sulfuric acid and 1.5 mL of thionyl chloride was stirred and heated at reflux for 48 h; an additional 0.6 mL of $SOCl_2$ was added in portions during the period of reflux. The reaction mixture was cooled (ice bath), and solid sodium bicarbonate was added. The neutralized solution was concentrated under diminished pressure, and the residue was partitioned between ether and water. The ether extract was dried (Na_2SO_4) and concentrated to afford methyl 4-amino-2,5-dimethylpyrimidine-6-carboxylate (**19**) as an off-white solid: yield 2.7 g (66%); IR (KBr) 3400, 3260, 1730, 1605, 1440, 1420, 1370, 1220 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.20 (s, 3 H), 2.50 (s, 3 H), 3.95 (s, 3 H).

Methyl 4-Acetamido-2,5-dimethylpyrimidine-6-carboxylate (20). A stirred solution of 2.7 g (14.9 mmol) of methyl 4-amino-2,5-dimethylpyrimidine-6-carboxylate (**19**) in 30 mL of pyridine and 40 mL of chloroform was treated dropwise with 10 mL of acetyl chloride. The reaction mixture was heated and stirred overnight and then stirred at room temperature for an additional 24 h. The reaction mixture was poured onto ice, and the resulting mixture was extracted with portions of chloroform. The combined chloroform extract was dried (Na_2SO_4) and concentrated, and the dark-colored residue was triturated with hot petroleum ether. The petroleum ether extract was concentrated, affording the desired amide as a yellow solid that could not be purified conveniently by crystallization: yield 1.9 g (57%); IR (KBr) 1735, 1660, 1430, 1360, 1260 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 2.30 (s, 6 H), 2.65 (s, 3 H), 4.02 (s, 3 H).

Ethyl 4-Azido-2,5-dimethylpyrimidine-6-carboxylate (21). To 230 mg (1.07 mmol) of ethyl 4-chloro-2,5-dimethylpyrimidine-6-carboxylate (**11**) in 3.0 mL of dimethylformamide was added 97 mg (1.5 mmol) of sodium azide. The resulting solution was stirred at room temperature over a period of 18 h, during which time a white precipitate formed. The reaction mixture was concentrated under diminished pressure, and the residue was triturated with ethyl acetate. The ethyl acetate extract was washed with water and dried. Concentration of the extract afforded a residue that crystallized from hexane as colorless needles: yield 235 mg (99%); mp 104–105 °C; IR (KBr) 2980, 1705, 1620, 1500, 1460, 1410, 1380, 1305 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.45 (t, 3 H), 2.95 (s, 3 H), 3.16 (s, 3 H), 4.50 (s, 3 H); mass spectrum, m/e 221, 193, 192 ($M^+ - N_3$), 177, 176, 149.

Ethyl 4-Amino-2,5-dimethylpyrimidine-6-carboxylate (22). A solution of 100 mg (0.43 mmol) of ethyl 4-azido-2,5-dimethylpyrimidine-6-carboxylate (**21**) in 100 mL of ethanol was treated with 100 mg of 5% palladium-on-carbon and shaken at room temperature for 10 h under 2 atm of H_2. The catalyst was filtered, and the solution was concentrated, affording colorless crystals of ethyl 4-amino-2,5-dimethylpyrimidine-6-carboxylate (**22**), which slowly darkened on standing: yield 86 mg (97%); mp 148 °C; IR (KBr) 3330, 3150, 1740, 1650, 1560, 1415, 1225 cm^{-1}; NMR ($CDCl_3$) δ 1.41 (t, 3 H), 2.10 (s, 3 H), 2.50 (s, 3 H), 4.40 (q, 2 H), 5.80 (s, 2 H, exchanged with D_2O).

Reaction of Pyrimidine 8 with Trimethylsilyl Iodide. A solution of pyrimidine **8** (32 mg, 0.133 mmol) and trimethylsilyl iodide (90%, 5 μL, 2.5 equiv) in 0.5 mL of $CDCl_3$ was sealed in a 5-mm NMR tube under N_2 and heated to 35 °C for 120 h. ^1H NMR analysis indicated nearly complete (~92%) loss of the resonance at 4.06 ppm (CO_2CH_3) and the appearance and increase of a peak at 2.15 ppm, corresponding to CH_3I. There was no evidence for the formation of C_2H_5I. Upon removal of volatile components and addition of water, a ^1H NMR spectrum identical with that of pyrimidine **7** was observed.

Reaction of Pyrimidine 8 with Lithium Methylmercaptide. A solution of 169 mg (0.7 mmol) of pyrimidine **8** and 38 mg (0.7 mmol) of lithium methylmercaptide[25] in 800 μL of DMF was heated at 100 °C for 20 h. The reaction mixture was cooled to 0 °C and treated with 3 mL of ether, and the resulting suspension was filtered to afford the lithium salt of ethyl 2-carboxy-5-methyl-4-oxopyrimidine-6-carboxylate (**24**): yield 27 mg (17%); NMR (D_2O, DSS) δ 1.38 (t, 3 H, J = 7.0 Hz), 2.20 (s, 3 H), 4.40 (q, 2 H, J = 7.0 Hz). The filtrate was concentrated and dried to give methyl 6-(carboethoxy)-5-methyl-4-pyrimidine-2-thiocarboxylate (**25**) as an oil that solidified on standing: yield 94 mg (53%); NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.40 (t, 3 H, J = 7.0 Hz), 2.32 (s, 3 H), 3.56 (s, 3 H), 4.37 (q, 2 H, J = 7.0 Hz); silica gel TLC (10:1 $CHCl_3$–CH_3OH) R_f 0.64.

Reaction of Pyrimidine 8 with Lithium *p*-Tolylmercaptide. Pyrimidine **8** (192 mg, 0.8 mmol) and lithium *p*-tolylmercaptide (prepared from 0.8 mmol of *p*-tolylmercaptan and 0.8 mmol of *n*-butyllithium in ether at 0 °C) were combined in 1.0 mL of DMF and heated at 100 °C for 20 h. Workup afforded 107 mg (43%) of ethyl 2-carboxy-5-methyl-4-oxopyrimidine-6-carboxylate and 54 mg (19%) of *p*-tolyl 6-(carboethoxy)-5-methyl-4-oxopyrimidine-2-thiocarboxylate: NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.40 (t, 3 H, J = 7.0 Hz), 2.33 (s, 6 H), 4.43 (q, 2 H, J = 7.0 H), 7.10 and 7.40 (AB pattern, 4 H, J = 8.0 Hz).

Ethyl 2-Carboxamido-5-methyl-4-oxopyrimidine-6-carboxylate (26). A solution of 619 mg (2.57 mmol) of ethyl 2-(carbomethoxy)-5-methyl-4-oxopyrimidine-6-carboxylate (**8**) in 13 mL of methanol was cooled in an ice bath and saturated with anhydrous ammonia for 30 min. The solution was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was then cooled to 0 °C and the white precipitate of pyrimidine **26** (ammonium salt) was filtered and air-dried: yield 451 mg (72%); mp 180–181.5 °C; IR (Nujol) 3360, 1740, 1720, 1660 (br), 1570 cm^{-1}; NMR (D_2O, external $(CH_3)_4Si$) δ 1.28 (t, 3 H, J = 7.0 Hz), 2.07 (s, 3 H), 4.31 (q, 2H, J = 7.0 Hz); mass spectrum, m/e 225 (M^+), 196, 179, 151.

Ethyl 2-(*N*-Benzylcarboxamido)-5-methyl-4-oxopyrimidine-6-carboxylate (27). A solution of 835 mg (7.65 mmol) of pyrimidine **8** and 0.84 mL (7.65 mmol) of benzylamine in 3.5 mL of methanol was stirred at 25 °C for 36 h. The resulting suspension was treated with 5 mL of 5 N hydrochloric acid and

then extracted with ethyl acetate (3 × 30 mL). The combined extract was washed with 1 N hydrochloric acid (1 × 10 mL), water (3 × 10 mL), and brine (1 × 10 mL). The organic phase was dried ($MgSO_4$) and concentrated under diminished pressure to afford **27** as a white solid: yield 1.03 g (97%); mp 129–131 °C after crystallization from ethyl acetate–hexane; IR (KBr) 1728, 1663, 1601 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.37 (t, 3 H, J = 7.0 Hz), 2.28 (s, 3 H), 4.36 (q, 2 H, J = 7.0 Hz), 4.53 (d, 2 H, J = 8.4 Hz), 7.26 (s, 5 H), 8.17 (br t, 1 H, J = 8.4 Hz); mass spectrum, m/e 315, 270, 208, 106.

5-Methyl-4-oxopyrimidine-2,6-bis(*N*,*N*-dimethylcarboxamide) (28). A solution of 471 mg (1.96 mmol) of pyrimidine **8** in 2 mL of 25% aqueous dimethylamine was stirred at 25 °C for 36 h. The volatile components of the reaction mixture were removed under diminished pressure, leaving pyrimidine **28** as an off-white powder in quantitative yield: NMR (D_2O, external $(CH_3)_4Si$) δ 1.81 (s, 3 H), 2.46 (s, 12 H).

Ethyl 5-Methyl-2-(pyrrolidinylcarbonyl)-4-oxopyrimidine-6-carboxylate (29). A solution of 38 mg (0.16 mmol) of ethyl 2-(carboxymethyl)-5-methyl-4-oxopyrimidine-6-carboxylate (**8**) and 24 mg (0.34 mmol) of pyrrolidine in 350 μL of *tert*-butyl alcohol was heated at reflux for 4 h. The cooled reaction mixture was treated with 20 mL of ethyl acetate and then washed successively with 1 N hydrochloric acid (3 × 5 mL) and water (3 × 5 mL). The organic phase was dried ($MgSO_4$) and concentrated under diminished pressure to afford pyrimidine **29** as a white solid: yield 31 mg (70%); mp 105–106 °C; IR (KBr) 1760, 1720, 1650, 1634, 1595 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.38 (t, 3 H, J = 7.0 Hz), 1.80–2.13 (m, 4 H), 2.30 (s, 3 H), 3.68 (br t, 2 H, J = 7.5 Hz), 4.10 (br t, 2 H, J = 7.5 Hz), 4.38 (q, 2 H, J = 7.0 Hz); mass spectrum, m/e 279 (M^+), 251, 234, 206, 70.

Ethyl 4-Chloro-2-cyano-5-methylpyrimidine-6-carboxylate (30). A solution of 385 mg (1.59 mmol) of ethyl 2-carboxamido-5-methyl-4-oxopyrimidine-6-carboxylate (**26**) in 4 mL of $POCl_3$ was heated at 100 °C for 30 min, during which time a white precipitate formed. Excess $POCl_3$ was removed under diminished pressure, and the residue was partitioned between $CHCl_3$ (30 mL) and water (10 mL). The chloroform extract was washed successively with water (2 × 5 mL) and brine (1 × 5 mL) and dried ($MgSO_4$). The solution was concentrated to afford ethyl 4-chloro-2-cyano-5-methylpyrimidine-6-carboxylate (**30**) as a liquid: yield 348 mg (97%); IR (neat) 1740 (br), 1530 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.45 (t, 3 H, J = 7.5 Hz), 2.63 (s, 3 H), 4.16 (q, 2 H, J = 7.5 Hz); mass spectrum, m/e 225 (M^+), 196, 179, 153, 126, 100.

2-(2-Hydroxy-3,3,3-trichloropropyl)-5-methyl-4-oxopyrimidine-6-carboxylic Acid (31). To 5.0 g (30 mmol) of anhydrous 6-carboxy-2,5-dimethyl-4-oxopyrimidine were added 12 mL of dry pyridine and 3.1 mL (32 mmol) of chloral. The reaction mixture was heated and stirred for 44 h at 85 °C. The dark liquid was concentrated to a tar, dissolved in ethanol, and adsorbed onto 25 g of silica gel. This dried material was applied to a column of silica gel (100 g) preequilibrated with diethyl ether. Elution with ether and ethyl acetate afforded an orange oil which solidifed after codistillation of portions of benzene; yield 6.3 g (67%). The light orange solid could be crystallized from ethyl acetate to give off-white crystals of 2-(2-hydroxy-3,3,3-trichloropropyl)-5-methyl-4-oxopyrimidine-6-carboxylic acid: mp 190–192 °C (lit.[19] mp 193 °C); λ_{max} (pH 1) 272 nm, 232; λ_{max} (pH 7) 272, 228; λ_{max} (pH 10) 268; NMR (Me_2SO-d_6, $(CH_3)_4Si$) δ 1.98 (s, 3 H), 2.60–2.63, 4.45 (ABX pattern).

5-Methyl-2-(3,3,3-trichloro-*trans*-1-propenyl)-4-oxopyrimidine-6-carboxylic Acid (32). To 5.0 g (30 mmol) of 2-(2-hydroxy-3,3,3-trichloropropyl)-5-methyl-4-oxopyrimidine-6-carboxylic acid was added 50 mL of warm pyridine and 50 mL of acetic anhydride. The reaction mixture was stirred in a stoppered flask overnight at room temperature, and the dark liquid was concentrated to a tar, dissolved in ethanol, and absorbed onto 25 g of silica gel. This dried material was applied to a column of silica gel (100 g) that had been preequilibrated with ethyl acetate. Elution with 800 mL of ethyl acetate and subsequent concentration of the eluant afforded a yellow solid: yield 5.0 g (85%); mp 158–162 °C. After two crystallizations from ethanol–water, the compound melted at 205.5–206.5 °C (lit.[19] mp 177 °C); the NMR (Me_2SO-d_6, $(CH_3)_4Si$) agreed with the published[19] data: δ 2.16 (s, 3 H), 6.89, 7.67 (AB pattern, 2 H); λ_{max} (C_2H_5OH, pH 1) 312 nm (ε 8600), 258 (5200); λ_{min} 274 (5700); λ_{max} (C_2H_5OH, pH 7) 311 (8100), 260 (br, 6400); λ_{min} 277 (5900); λ_{max} (C_2H_5OH, pH 10) 312 (6700), 260 (sh, 8800), 232 (7100); λ_{min} 285 (4500), 225 (6500).

Anal. Calcd for $C_9H_7N_2O_3Cl_3$: C, 36.33; H, 2.37. Found: C, 36.51; H, 2.24.

Direct Conversion of 3 to 5-Methyl-2-(3,3,3-trichloro-*trans*-1-propenyl)-4-oxopyrimidine-6-carboxylic Acid (32). To 5.0 g (30 mmol) of anhydrous 2,5-dimethyl-4-oxopyrimidine-6-carboxylic acid (**3**) were added 12 mL of dry pyridine and 3.1 mL (32 mmol) of chloral. The reaction mixture was heated at 85 °C for 44 h and then concentrated to afford a black tar. This material was dissolved in 50 mL of dry pyridine and treated with 50 mL of acetic anhydride. The combined solution was maintained overnight at room temperature and then concentrated to afford a residue which was purified by silica gel chromatography to afford pyrimidine **32**: yield 5.34 g (61%); mp 189–191 °C.

3-(6-Carboxy-5-methyl-4-oxopyrimidin-2-yl)acrylic Acid (33). To 40 mL of concentrated H_2SO_4 was added 15.5 g (52.1 mmol) of 5-methyl-2-(3,3,3-trichloro-*trans*-1-propenyl)-4-oxopyrimidine-6-carboxylic acid (**32**). The slurry was stirred and heated at 70 °C for 18 h. After being chilled in an ice bath, the reaction mixture was poured onto crushed ice and shaken with diethyl ether. The resulting precipitate was filtered and dried to afford a tan solid, yield 5.60 g (48%); an additional 2.70 g of product was recovered by continuous extraction of the acidic filtrate with diethyl ether: total 8.30 g (71%) of crude product; mp 238–248 °C. Crystallization from boiling water (decolorization) afforded 3-(6-carboxy-5-methyl-4-oxopyrimidin-2-yl)acrylic acid as off-white crystals: mp 257–258 °C; λ_{max} (pH 1) 312 nm, 225 (sh); λ_{max} (pH 7) 308, 227; λ_{max} (pH 12) 302, 258 (sh); NMR (Me_2SO-d_6, $(CH_3)_4Si$) δ 2.00 (s, 3 H), 6.95 (AB pattern, J = 12 Hz, 2 H).

Ethyl *trans*-3-[6-(Carboethoxy)-5-methyl-4-oxopyrimidin-2-yl]acrylate (34). To 45 mL of triethyl orthoformate was added 1.15 g (5.13 mmol) of 3-(6-carboxy-5-methyl-4-oxopyrimidin-2-yl)acrylic acid (**33**), and the mixture was heated at reflux (drying tube) for 3.5 h, but solid still remained. TLC revealed that some unreacted acrylic acid was still present; hence, the reaction mixture was concentrated to dryness, and the residue was treated with fresh triethyl orthoformate. An additional 2 h of heating served to dissolve the remaining solid. Evaporation afforded a tan semisolid consisting of only one major substance as judged by silica gel TLC (4:1 $CHCl_3$–MeOH, R_f 0.85); yield 1.30 g (92%). Crystallization from methanol afforded pyrimidine **34** as colorless needles: mp 139–141 °C; λ_{max} (C_2H_5OH, pH 1) 318 nm (ε 8800), 227 (sh, 16 400); λ_{min} 283 (5700); λ_{max} (C_2H_5OH, pH 7) 318 (8700), 227 (sh, 16 400); λ_{min} 283 (5700); λ_{max} (C_2H_5OH, pH 10) 323 (6700), 242 (21 900); λ_{min} 298 (5200), 229 (19 600); NMR (CCl_4, $(CH_3)_4Si$) δ 1.35 (m, 6 H), 2.20 (s, 3 H), 4.22 (m, 4 H), 7.17 (s, 2 H); NMR (acetone-d_6, $(CH_3)_4Si$) δ 1.28 (m, 6 H), 2.06 (m, overlap with acetone resonance), 4.22 (m, 4 H), 7.09 (AB pattern, J = 15 Hz, 2 H); mass spectrum, m/e 280 (M^+), 279, 233, 206, 205, 204, 177, 160, 134, 133, 132, 126, 98.

Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75. Found: C, 55.74; H, 5.73.

Ethyl 3-[6-(Carboethoxy)-5-methyl-4-oxopyrimidin-2-yl]-propionate (35). A solution containing 9.77 g (34.9 mmol) of pyrimidineacrylate **34** in 200 mL of ethyl acetate and 50 mL of ethanol was treated with 800 mg of 1% palladium-on-carbon and hydrogenated at 30 psi of H_2 on a Parr apparatus for 12 h. The reaction mixture was filtered through a Celite pad, which was rinsed with ethyl acetate. The combined filtrate was concentrated under diminished pressure to afford ethyl 3-[6-(carboethoxy)-5-methyl-4-oxopyrimidin-2-yl]propionate (**35**) as a fluffy white solid, yield 9.85 g (100%). Recrystallization from ethanol provided colorless microcrystals of **35**: mp 124–125 °C; IR (Nujol) 1725, 1650, 1580 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.22 (t, J = 7.0 Hz, 3 H), 1.37 (t, J = 7.0 Hz, 3 H), 2.14 (s, 3 H), 2.78–2.98 (m, 4 H), 4.08 (q, J = 7.0 Hz, 2 H), 4.32 (q, J = 7.0 Hz, 2 H).

Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.30; H, 6.42. Found: C, 55.01; H, 6.18.

Ethyl 3-[6-(Carboethoxy)-5-methyl-4-oxopyrimidin-2-yl]-3,3-dibromopropionate (36). A stirred solution of 425 mg (1.5 mmol) of ethyl 3-[6-(carboethoxy)-5-methyl-4-oxopyrimidin-2-yl)propionate (**35**) and 512 mg (3.76 mmol) of sodium

acetate in 3 mL of glacial acetic acid was treated with 169 μL (3.3 mmol) of bromine. The reaction mixture was stirred at room temperature for 40 h. Ethyl acetate (50 mL) was added to the reaction mixture, which was washed with 1% sodium bisulfite (1 × 10 mL), water (3 × 10 mL), and brine (1 × 10 mL). The dried ($MgSO_4$) organic phase was concentrated under diminished pressure to afford pyrimidine **36** as a white solid: yield 607 mg (93%); mp 93.5–94.5 °C; IR (KBr) 1740, 1725, 1650, 1600 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.20 (t, J = 7.0 Hz, 3 H), 1.33 (t, J = 7.0 Hz, 3 H), 2.21 (s, 3 H), 4.00 (s, 2 H), 4.18 (q, J = 7.0 Hz, 4 H); mass spectrum, m/e 442, 440, 438, 397, 396, 395, 394, 393, 392, 361, 359, 315, 313, 287, 286, 285, 284, 259, 258, 257, 256; silica gel TLC (10:1 $CHCl_3$–CH_3OH) R_f 0.64.

(*E*)- and (*Z*)-Ethyl 3-[6-(Carboethoxy)-5-methyl-4-oxopyrimidin-2-yl]-3-bromoacrylates (38 and 39). To a solution containing 70 mg (0.16 mmol) of ethyl 3-[6-(carboethoxy)-5-methyl-4-oxopyrimidin-2-yl]-3,3-dibromopropionate (**36**) in 1.0 mL of absolute ethanol was added 150 mg (1.4 mmol) of sodium carbonate. The reaction mixture was stirred at room temperature for 40 h and then treated with 20 mL of ethyl acetate and 5 mL of saturated ammonium chloride solution. The ethyl acetate solution was washed with saturated salt solution and dried over $MgSO_4$. The dried solution was concentrated under diminished pressure, and the residue was dissolved in 30 mL of absolute ethanol and decolorized with activated charcoal. Concentration of the solution afforded a 7:1 mixture of vinyl bromides (*E*)-**38** and (*Z*)-**39** in quantitative yield. The major isomer (**38**) was isolated as a white solid by preparative TLC on silica gel (10:1 $CHCl_3$–CH_3OH): mp 102.5–104.5 °C; IR (Nujol) 1737, 1720, 1660–1650 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.18 (t, J = 7.0 Hz, 3 H), 1.41 (t, J = 7.0 Hz, 3 H), 2.33 (s, 3 H), 4.15 (q, J = 7.0 Hz, 2 H), 4.46 (q, J = 7.0 Hz, 2 H), 6.86 (s, 1 H); mass spectrum, m/e 360, 358, 314, 312, 286, 284, 177, 90; silica gel TLC (10:1 $CHCl_3$–CH_3OH) R_f 0.46.

A mixture of vinyl bromides **38** and **39** was dissolved in 90% sulfuric acid, and the solution was stirred at 0 °C for 2 h. The reaction mixture was poured onto ice and extracted with ethyl acetate. The combined ethyl acetate extract was washed with saturated NaCl solution and dried ($MgSO_4$). Concentration of the solution afforded a 1:7 mixture of vinyl bromides **38** and **39**, from which **39** was isolated by preparative TLC: mp 107–108 °C; IR (Nujol) 1745, 1729, 1670–1655 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.35 (t, J = 7.0 Hz, 3 H), 1.43 (t, J = 7.0 Hz, 3 H), 2.31 (s, 3 H), 4.35 (q, J = 7.0 Hz, 2 H), 4.50 (q, J = 7.0 Hz, 2 H), 7.88 (s, 1 H); mass spectrum, m/e 360, 358, 314, 312, 286, 284, 205, 177; silica gel TLC (10:1 $CHCl_3$–CH_3OH) R_f 0.54.

Ethyl 3-[6-(Carboethoxy)-4-chloro-5-methylpyrimidin-2-yl]propionate (40). A solution of 5.04 g (17.85 mmol) of ethyl 3-[6-(carboethoxy)-5-methyl-4-oxopyrimidin-2-yl)propionate (**35**) in 30 mL of freshly distilled phosphorous oxychloride was heated at reflux for 30 min. The cooled reaction mixture was concentrated to dryness under diminished pressure, and the dark-colored residue was dissolved in 100 mL of chloroform and washed with water (3 × 20 mL) and brine (1 × 20 mL). The dried ($MgSO_4$) $CHCl_3$ solution was concentrated, and the residue was dissolved in 50 mL of 3:7 ethyl acetate–petroleum ether and filtered through a layer of silica gel. The silica gel was washed with 100 mL of fresh solvent, and the combined filtrate was concentrated under diminished pressure to afford chloropyrimidine **40** as a viscous yellow oil: yield 5.13 g (96%); IR (neat) 1740, 1735, 1560, 1530 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.23 (t, J = 7.0 Hz, 3 H), 1.41 (t, J = 7.0 Hz, 3 H), 2.41 (s, 3 H), 2.83 (t, J = 6.0 Hz, 2 H), 3.26 (t, J = 6.0 Hz, 2 H), 4.11 (q, J = 7.0 Hz, 2 H), 4.45 (q, J = 7.0 Hz, 2 H); mass spectrum, m/e 302, 300, 257, 255, 229, 227, 182, 153.

Ethyl 3-[4-Azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]propionate (41). A solution containing 5.11 g (17.0 mmol) of ethyl 3-[6-(carboethoxy)-4-chloro-5-methylpyrimidin-2-yl]-propionate (**40**) and 1.66 g (25.6 mmol) of sodium azide in 50 mL of DMF was stirred at 25 °C for 18 h. Ethyl acetate (200 mL) was added, and the solution was washed with water (3 × 50 mL) and brine (1 × 50 mL). The dried ($MgSO_4$) solution was concentrated, and the yellow residue was crystallized from 1:3 ethyl acetate–petroleum ether to afford azidopyrimidine **41** as colorless needles: yield 4.46 g (86%); mp 60–61 °C; IR (Nujol) 1725, 1620 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.26 (t, J = 7.0 Hz, 3 H), 1.48 (t, J = 7.0 Hz, 3 H), 2.93 (s, 3 H), 3.13 (t, J = 6.0 Hz, 2 H), 3.81 (t, J = 6.0 Hz, 2 H), 4.16 (q, J = 7.0 Hz, 2 H), 4.50 (q, J = 7.0 Hz, 2 H).

Anal. Calcd for $C_{13}H_{17}N_5O_4$: C, 50.80; H, 5.57; N, 22.79. Found: C, 50.41; H, 5.37; N, 22.60.

Ethyl 3-[4-Azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]-3-bromopropionate (42). A solution of azidopyrimidine **41** (1.03 g, 3.35 mmol) and dioxane dibromide (0.87 g, 3.51 mmol) in 65 mL of CCl_4 was heated at reflux for 1 h. The cooled solution was concentrated under diminished pressure, and the residue was dissolved in 30 mL of 3:7 ethyl acetate–petroleum ether and filtered through a layer of silica gel. The silica gel was washed with 60 mL of fresh solvent, and the combined filtrate was concentrated to afford **42** (an equilibrium mixture of azide and tetrazole) as a viscous oil: yield 1.29 g (100%); IR ($CHCl_3$) 2150 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.23 (t, J = 7.0 Hz, 3 H), 1.41, 1.43 (t, J = 7.0 Hz, 3 H), 2.25, 2.96 (s, 3 H), 3.13–3.83 (m, 2 H), 4.10 (q, J = 7.0 Hz, 2 H), 4.41, 4.44 (q, J = 7.0 Hz, 2 H), 5.41 (t, J = 8.0 Hz, 0.6 H), 6.06 (dd, J = 9.0, 6.0 Hz, 0.4 H); mass spectrum, m/e 386, 342, 313, 284, 232, 186, 160.

Ethyl 3-[4-Azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]-3-(benzylamino)propionate (43). A reaction mixture containing 120 mg (0.32 mmol) of bromopyrimidine **42**, 40 μL (0.37 mmol) of benzylamine, and 32 mg (3.9 mmol) of sodium bicarbonate in 2 mL of methanol was stirred at 25 °C for 1 h. The excess solvent was removed in vacuo, and the crude residue was fractionated by preparative silica gel TLC (3:7 ethyl acetate–hexane). The appropriate band (R_f 0.3) was extracted with the same solvent mixture, affording the desired pyrimidine (**43**) as a colorless oil: yield 54 mg (41%); NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.36 (t, J = 7.0 Hz, 3 H), 1.56 (t, 3 H, J = 7.0 Hz), 2.3 (br s, 1 H), 3.1 (s, 3 H), 3.68–4.16 (m, 5 H), 4.3 (q, J = 7.0 Hz, 2 H), 4.61 (q, J = 7.0 Hz, 2 H), 7.28 (m, 5 H); mass spectrum, m/e 384 (M^+ – 28), 339, 192, 191.

D,L-N^{α}-(Carbobenzyloxy)-β-aminoalaninamide (44). A solution of 4.0 g (14.7 mmol) of the methyl ester of N^{α}-(carbobenzyloxy)-β-chloroalanine[30] in 10 mL of ethanol was saturated with anhydrous ammonia at 0 °C and then maintained at room temperature for 3 days. The ethanolic solution was concentrated, and the residue was triturated with ether and hexane, affording D,L-N^{α}-(carbobenzyloxy)-β-aminoalaninamide as a white solid that was purified further by precipitation from CH_3OH–$(C_2H_5)_2O$: yield 3.4 g (84%); mp 176 °C (melting point of free base 80 °C); IR (KBr) 3300 (br), 1670, 1590, 1530, 1260 cm^{-1}; NMR (CD_3OD, $(CH_3)_4Si$) δ 3.85 (m, 1 H), 4.40 (d, 2 H), 4.50 (s, 2 H), 6.70 (s, 5 H).

Ethyl 3-[4-Azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]-3-[[2-[[(benzyloxy)carbonyl]amino]-2-carboxamidoethyl]amino]propionate (45). A solution containing 30 mg (0.08 mmol) of bromopyrimidine **42**, 22 mg (0.08 mmol) of D,L-N^{α}-(carbobenzyloxy)-β-aminoalaninamide hydrochloride, and 16 mg (0.17 mmol) of sodium bicarbonate in 1.0 mL of methanol was stirred overnight at room temperature. The excess solvent was removed under diminished pressure, and the residue was partitioned between ethyl acetate and water. The ethyl acetate extract was dried ($MgSO_4$) and concentrated under diminished pressure. Purification of **45** was accomplished by preparative TLC on silica gel (9:1 $CHCl_3$–CH_3OH); the major band (R_f 0.17) contained 13 mg (30%) of the desired product: NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.28 (t, J = 7.0 Hz, 3 H), 1.5 (t, J = 7.0 Hz, 3 H), 2.9 (s, 3 H), 3.7–4.42 (m, 5 H), 4.25 (q, J = 7.0 Hz, 2 H), 4.5 (q, J = 7.0 Hz, 2 H), 5.13 (s, 2 H), 6.93 (br s, 1 H), 7.38 (s, 5 H).

Ethyl 3-Amino-3-[4-azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]acrylate (47) and Ethyl 3-Azido-3-[4-azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]propionate (46). (A) In Dimethylformamide. A solution of 778 mg (2.01 mmol) of pyrimidine **42** and 157 mg (2.40 mmol) of sodium azide in 3 mL of DMF was stirred at 25 °C under N_2 for 18 h. The solution was treated with 20 mL of ethyl acetate and then extracted successively with water (3 × 5 mL) and brine (1 × 5 mL). The dried ($MgSO_4$) solution was concentrated under diminished pressure, and the residue was filtered through a layer of silica gel (elution with 100 mL of 1:1 ethyl acetate–petroleum ether). The solvent was concentrated, and the residue was precipitated from hot ethanol, affording enaminopyrimidine **47** as a pale yellow solid: yield 510 mg (79%); mp 80–81 °C; λ_{max} (C_2H_5OH) 328 nm, 257; IR ($CHCl_3$)

3472, 3322, 2105, 1712, 1644, 1607, 1536 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.13 (t, J = 7.0 Hz, 3 H), 1.41 (t, J = 7.0 Hz, 3 H), 2.26 (s, 3 H), 4.18 (q, J = 7.0 Hz, 2 H), 4.40 (q, J = 7.0 Hz, 2 H), 6.00 (s, 1 H), 7.0 (br, 1 H); mass spectrum, m/e 320 (M^+), 275, 247, 246, 201, 200, 174, 134.

Anal. Calcd for $C_{13}H_{16}N_6O_4$: C, 48.74; H, 5.03. Found: C, 48.79; H, 4.97.

(B) In Methanol. A solution of 87 mg (0.225 mmol) of pyrimidine **42** and 16 mg (0.246 mmol) of sodium azide in 0.3 mL of methanol was heated at 50 °C for 6 h. The solution was treated with 20 mL of ethyl acetate and then extracted with water (3 × 5 mL) and brine (1 × 5 mL). The ethyl acetate layer was dried ($MgSO_4$) and concentrated under diminished pressure to afford a residue which was purified by preparative silica gel TLC (3:7 ethyl acetate–petroleum ether). The major fraction (32 mg, ~ 40%) consisted of a 1:1 mixture of compound **47** and diazidopyrimidine **46**; NMR ($CDCl_3$, partial) δ 2.30 (s, 3 H), 2.83–3.16 (m, 2 H), 4.95 (dd, J = 8.0, 6.0 Hz).

Ethyl 3-Amino-3-[4-azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]propionate (48). To a stirred solution of 549 mg (1.72 mmol) of ethyl 3-amino-3-[4-azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]acrylate (**47**) in 3.4 mL of methanol and 1.2 mL of tetrahydrofuran containing a trace amount of bromcresol green was added sufficient 2 N HCl to maintain a yellow color. Sodium cyanoborohydride (340 mg, 3.44 mmol) was added in portions over a period of 30 min, along with enough acid to maintain the pH at 3–4. After the reaction mixture was stirred at room temperature for an additional 30 min, 30 mL of $CHCl_3$ was added, and the resulting solution was washed successively with 1 N sodium bicarbonate solution (4 × 10 mL), water (3 × 10 mL), and brine (1 × 10 mL). The organic phase was dried ($MgSO_4$) and concentrated under diminished pressure. The residue was dissolved in ethyl acetate and filtered through a layer of silica gel; concentration of the filtrate provided ethyl 3-amino-3-[4-azido-6-(carboethoxy)-5-methylpyrimidin-2-yl]-propionate (**48**) as a yellow oil: yield 440 mg (80%); IR (neat) 3390, 2150, 1740, 1730, 1618 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.22, 1.24 (t, J = 7.0 Hz, 3 H), 1.46 (t, J = 7.0 Hz, 3 H), 2.22, 2.94 (s, 3 H), 2.83 (br s, 2 H, exchanged with D_2O), 3.11, 3.19 (d, J = 7.0 Hz, 2 H), 4.12 (q, J = 7.0 Hz, 2 H), 4.48 (q, J = 7.0 Hz, 2 H), 5.21 (t, J = 7.0 Hz, 1 H).

Ethyl 3-Amino-3-[4-amino-6-(carboethoxy)-5-methylpyrimidin-2-yl]propionate (49). A solution of 440 mg (1.37 mmol) of pyrimidine **48** in 10 mL of 5:1 ethanol–ethyl acetate was treated with 60 mg of 10% palladium-on-charcoal and hydrogenated (4 atm) on a Parr apparatus for 4 h. The suspension was filtered (Celite), and the filtrate was concentrated under diminished pressure to afford an oily residue. The residue was purified by preparative TLC on silica gel (ethyl acetate), affording ethyl 3-amino-3-[4-amino-6-(carboethoxy)-5-methylpyrimidin-2-yl]-propionate (**49**) as a colorless oil: yield 35 mg (12%); IR (neat) 3340, 3200, 1725, 1655, 1635, 1575 cm^{-1}; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.23 (t, J = 7.0 Hz, 3 H), 1.40 (t, J = 7.0 Hz, 3 H), 2.20 (s, 3 H), 2.70–2.95 (m, 2 H), 4.13 (q, J = 7.0 Hz, 2 H), 4.40 (q, J = 7.0 Hz, 2 H), 5.03 (dd, J = 8.0 Hz, 1 H), 5.46 (br s, 2 H, exchanged with D_2O); silica gel TLC (ethyl acetate) R_f 0.66.

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Pyrrolo[2,3-*d*]pyrimidine Nucleoside Antibiotic Analogues. Synthesis via Organopalladium Intermediates Derived from 5-Mercuritubercidin

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C-5-substituted pyrrolo[2,3-*d*]pyrimidine nucleosides were synthesized via reactions of 5-mercuritubercidin (**4**). Palladium-catalyzed carbonylation of **4** in methanol gave 5-(methoxycarbonyl)tubercidin (**5**) which could be converted to the nucleoside antibiotic sangivamycin (**3**) by reaction with ammonia. Vinylogues **9** and **10** of sangivamycin and toyocamycin (**2**) were obtained by way of a Heck-type organopalladium olefin coupling reaction. 5-Mercuritubercidin and methyl acrylate in 0.1 M Li_2PdCl_4 in methanol gave (*E*)-5-[2-(methoxycarbonyl)-ethenyl]tubercidin (**7**) which on treatment with aqueous ammonia gave **9**. The vinylogue of toyocamycin was obtained directly from the reaction of acrylonitrile with Li_2PdCl_4 and **4** in *N*,*N*-dimethylformamide (DMF). Nucleoside **7** was converted to (*E*)-5-(2-bromoethenyl)tubercidin by hydrolysis with base followed by treatment with NBS in DMF. The coupling reactions with ethylene, 3-chloro-1-butene, and styrene were also investigated. Ethylene, 4, and 0.1 M Li_2PdCl_4 in methanol lead to 5-(1-methoxyethyl)tubercidin (**15**) and in water to tubercidin (**1**) and 5-(1-hydroxyethyl)tubercidin (**16**). The tubercidin was postulated to result from an acid-catalyzed retro-aldol-type fragmentation. Iodination of 5-mercuritubercidin gave 5-iodotubercidin (**23**).

In light of the biological activity displayed by tubercidin (**1**) and such C-5-substituted pyrrolo[2,3-*d*]pyrimidine nucleosides as 4-amino-5-cyano-7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (toyocamycin, **2**) and 4-amino-5-carboxamido-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (sangivamycin, **3**),[1,2] the preparation of additional members of this class is of interest. The introduction of a variety of C-5 substituents via transformations of the

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