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.

Acknowledgment. We thank Dr. Tomohisa Takita for discussing some of his experimental results prior to publication. We thank Dr. Heihachiro Arai and Mr. Mark Levin for assistance in optimization of certain synthetic transformations. This investigation was supported by Grant No. CA 22614, awarded by the National Cancer Institute, Department of Health, Education, and Welfare.

Registry No. **3**, 39875-10-0; **4**, 74536-25-7; **5**, 76480-50-7; **6**, 76480-51-8; **7**, 76480-52-9; **8**, 76480-53-0; **9**, 76480-54-1; **10**, 76480-55-2; **11**, 76498-32-3; **12**, 76480-56-3; **14**, 39875-13-3; **15**, 62907-95-3; **16**·2HCl, 76480-57-4; **17**, 76498-33-4; **18**, 72792-79-1; **19**, 76480-58-5; **20**, 76480-59-6; **21**, 76480-60-9; **22**, 76480-61-0; **23**, 76480-62-1; **24**, 76480-63-2; **25**, 76480-64-3; **26**, 76480-65-4; **27**, 76480-66-5; **28**, 76480-67-6; **29**, 76480-68-7; **30**, 76480-69-8; **31**, 39875-11-1; **32**, 76480-70-1; **33**, 76480-71-2; **34**, 76480-72-3; **35**, 75624-19-0; **36**, 76480-73-4; **38**, 76480-74-5; **39**, 76480-75-6; **40**, 76498-34-5; **41**, 75624-20-3; **42**, 76480-76-7; **43**, 76480-77-8; **44**, 76480-78-9; **44**·HCl, 76480-79-0; **45**, 76498-35-6; **46**, 76480-80-3; **47**, 76480-81-4; **48**, 76480-82-5; **49**, 76480-83-6; acetamidine hydrochloride, 51991-59-4; ethyl ethoxalylpropionate, 759-65-9; potassium 2,5-dimethyl-4-pyrimidine-6-carboxylate, 76480-84-7; lithium methylmercaptide, 35638-70-1; *p*-tolyl 6-(carboethoxy)-5-methyl-4-oxopyrimidine-2-thiocarboxylate, 76480-85-8; benzylamine, 100-46-9; dimethylamine, 124-40-3; pyrrolidine, 123-75-1; N^{α}-(carbobenzyloxy)-β-chloroalanine methyl ester, 56618-03-2.

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

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Received July 11, 1980

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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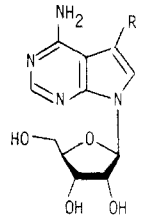


1 R = H

2 R = CN

3 R = $CONH_2$

cyano group of 2 has previously been described,[3] but no methods have heretofore been available for the direct introduction of side chains into the C-5 position of 1.

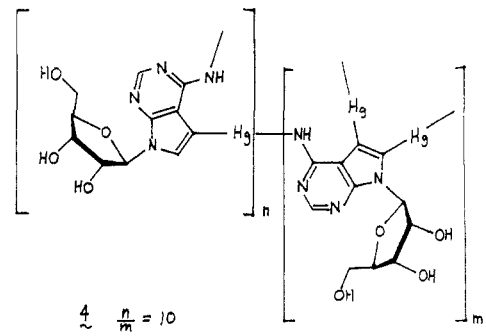
This laboratory has recently developed a method by which olefins can be coupled to organopalladium intermediates derived in situ from mercurated pyrimidine nucleosides.[4] Following this lead, we have explored the versatility of 5-mercuritubercidin[5] (4) as an intermediate for (1) palladium-catalyzed carbonylation, (2) the introduction of olefins via a Heck-type organopalladium olefin coupling reaction, and (3) halogenation at the C-5 position. The scope and limitation of these reactions are discussed in the present paper.

Results and Discussion

A major problem in development of methodology for introduction of carbon chains in tubercidin at C-5 was the synthesis of a well-defined, C-5-mercurated product. Mercuration of tubercidin is not selective enough to give a single product. Not only does mercuration occur at both C-5 and C-6 of the pyrrolo[2,3-*d*]pyrimidine nucleus but the resulting C-5 monomercurated and C-5, C-6 dimercurated products also are inseparable by ordinary chemical and physical means due to the polymeric nature of the product.[5] Presumably mercury is covalently linked at C-5,C-6 and either bound through N-1 or N-6 in resemblance to mercury binding to adenosine.[6-9]

We have favored N-6 binding in tubercidin on the basis of the absence of acetate ion in the mercurated products. Furthermore, washing with chloride ion does not introduce significant chloride in the mercurated product. Mercury binding at N-6 has been proposed as the predominant mode of binding above pH 7 for adenosine.[8,9] The symmetrical structure R_2Hg (C-5 to mercury to C-5 linkage) was considered unlikely on the basis of known organomercurial chemistry and the ratio of mercury to nucleoside (1:1).

At best we have routinely isolated a product from mercuration of tubercidin with 1 equiv of mercuric acetate which is approximately 90% C-5 mercurated and 10% C-5,C-6 dimercurated. This material, whose structure may be represented by 4, was used throughout these studies for further chemical transformations and shall for convenience be subsequently referred to as 5-mercuritubercidin. Despite its ill-defined nature, 4 has routinely given well-defined products and in many instances easily purified C-5-substituted tubercidin derivatives.



4 $\frac{n}{m} = 10$

A straightforward route for the introduction of a single carbon unit at C-5 of tubercidin is particularly desirable. Not only do the nucleoside antibiotics sangivamycin and toyocamycin have a one-carbon functional group at this position but the hypermodified tRNA bases, nucleoside Q and Q*, also have a methylene group at C-5 of a pyrrolo[2,3-*d*]pyrimidine nucleus.[10,11] We have found it possible to introduce a one-carbon functional group at C-5 in the oxidation states characteristic of both classes of compounds. The key reaction is the palladium-catalyzed carbonylation reaction first developed by Henry.[12] Aryl mercuric chlorides react at room temperature with carbon monoxide and palladium chloride in acetic acid to give carboxylic acids. In methanol solvent, the product is a methyl ester. Heck[13] and Larock[14] have explored and greatly expanded the scope of the reaction.

When mercuritubercidin and lithium palladium chloride were combined in methanol under a carbon monoxide atmosphere, slow conversion to 5-(methoxycarbonyl)-tubercidin (5) occurred (Scheme I). The yield was not high (24% after purification) but the method is both direct and simple. The methoxycarbonyl group can be further converted to other functional groups without protection of the 4-amino or sugar hydroxyls. Ammonolysis in aqueous ammonium chloride–ammonium hydroxide gave the nucleoside antibiotic sangivamycin (3). The only previous synthesis of 3 involved reaction of 5-cyano-6-bromotubercidin with ammonium hydroxide in 30% H_2O_2 followed by catalytic hydrogenolysis of the 6-bromo group.[15] 5-(Methoxycarbonyl)tubercidin has been obtained by refluxing sangivamycin in 10% H_2SO_4 in methanol.[16] Reduction of 5 with lithium borohydride in refluxing THF gave 5-(hydroxymethyl)tubercidin (6).[32] Uematsu and Suhadolnik previously accomplished this transformation by converting 5 to its 2′,3′-*O*-isopropylidene derivative and reducing this with $LiAlH_4$.[17] In light of the facility with which the hydroxy group of 5-(hydroxymethyl)uracil is replaced by amines,[18] it is possible that this is a viable approach to nucleoside Q and nucleoside Q* analogues. With 2-amino-7-(β-D-ribofuranosyl)-

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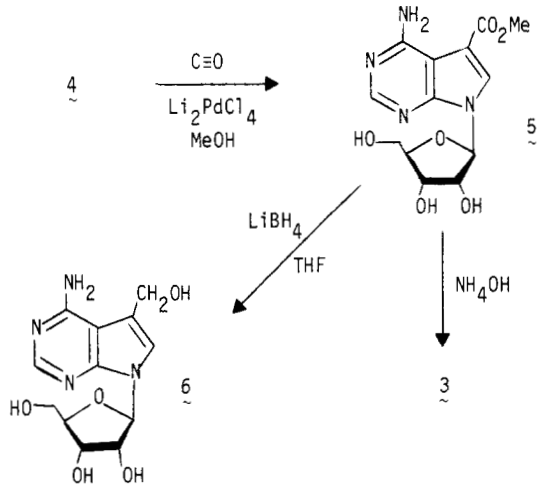
Scheme I



pyrrolo[2,3-*d*]pyrimidin-4-one as the precursor, the hydroxymethyl group could be introduced and coupling with (3*S*,4*R*,5*S*)-3-amino-4,5-dihydroxycyclopent-1-ene achieved in aqueous acid.[19] Or, alternatively, the hydroxymethyl group could be oxidized to an aldehyde which could be reductively aminated with an amine and sodium trihydrocyanoborate.[20]

The majority of synthetic compounds described in this paper were characterized by ^1H NMR, ^{13}C NMR, and elemental analysis. ^{13}C NMR has provided the most reliable data for making structure assignments (Table I). Chenon et al.[21] have established carbon chemical shifts for the pyrrolo[2,3-*d*]pyrimidine nucleosides **1–3**. Like these authors, we have determined ^{13}C NMR spectra with complete proton decoupling. Our data on a large number of C-5-substituted compounds (Table I) confirm the observations made by Chenon et al. The chemical shifts of the ribosyl carbons are for the most part invariant and unaffected by the structure of the C-5 substituent. The only heterocyclic carbon shifts significantly dependent on C-5 substitution are those of C-5 and C-6. Nucleosides **1–5** are illustrative. The carbon signals for C-2, C-4, C-4a, and C-7a fall within a 2-ppm range while those at C-5 vary from 83.2 ppm[21] for toyocamycin (**2**) to 115.5 ppm for 5-(hydroxymethyl)-tubercidin (**6**) and those at C-6 from 119.1 for **5** to 132.6 for toyocamycin. The relative magnitude and direction of the shifts parallel those observed in derivatives of benzene.[22] For example, both C-1 and C-2 of methyl benzoate are shifted downfield (2 and 1.2 ppm, respectively) from the carbon signal for benzene (128.5 ppm). The C-5 and C-6 resonances of 5-(methoxycarbonyl)-tubercidin (**5**) are shifted 6.5 and 7.0 ppm downfield, respectively, from the signals observed in tubercidin. In contrast, the C-1 and C-2 signals of benzyl alcohol fall at 141.0 and 126.9 ppm, respectively. These values represent shifts of 12.5 ppm downfield for C-1 and 1.6 ppm upfield for C-2. The corresponding carbons in 5-(hydroxymethyl)tubercidin show parallel shifts with respect to tubercidin. The C-5 resonance of **6** is shifted 16 ppm downfield while the C-6 resonance falls 3.2 ppm further upfield. Data for other tubercidin derivatives have also shown parallel and consistent results in comparison to ^{13}C NMR data on simpler model compounds.

The coupling reaction between the in situ generated, tubercidin-derived organopalladium intermediate and olefins was investigated to explore potential routes to a set of C-5-substituted tubercidin derivatives of interest as potentially biologically active compounds. Our initial goal has been realized in that many types of functional groups were found to be compatible with the reaction conditions and successfully led to products. The majority of the coupling reactions described here used olefins previously found to couple to 2′-deoxyuridine.[4] Yet there were sufficient differences to make an account of the tubercidin reactions of interest. To expand the methodology further, we examined the feasibility of applying other synthetic transformations to the C-5-substituted tubercidins that did not require nucleoside hydroxyl or amino protection.

Of α,β-unsaturated carbonyl compounds (and related derivatives), methyl acrylate and acrylonitrile could be coupled successfully, acrylamide coupled in very low yield, and acrolein gave no identifiable product. Methyl acrylate was previously shown to react with 5-(chloromercuri)-uridine in 0.1 M Li_2PdCl_4–methanol to give (*E*)-5-[2-(methoxycarbonyl)ethenyl]uridine in good yield.[4] The reaction of **4** with methyl acrylate in 0.1 M Li_2PdCl_4–methanol proceeded more slowly to give (*E*)-5-[2-methoxycarbonyl)ethenyl]tubercidin **7** (Scheme II). In addition, a second product, 5-[2-(methoxycarbonyl)-1-methoxyethyl]tubercidin (**8**), could be separated by chromatography. Typically the ratio of **7** to **8** was 6:1 or greater. The related α-methoxy compound had not been observed in the 2′-deoxyuridine reaction, but its occurrence can be explained in light of the results of other reactions run in methanol.[4]

Although no mechanistic studies were done in this instance, the schemes proposed by Heck[23] for the reaction of phenylmercuric acetate with propylene and Pd(II) in methanol and acetonitrile and the results of our studies[4] on the reaction of 5-(chloromercuri)-2′-deoxyuridine with propylene and Pd(II) lead us to propose the pathway shown in Scheme III. The mercuritubercidin complex **4** must undergo metal–metal exchange with palladium chloride or the methyl acrylate–palladium chloride π complex to give intermediate i. Insertion of methyl acrylate into the Pd–C σ bond proceeds regioselectively to give ii which through syn elimination of Pd–H leads to the π complex iii.

The predominant pathway involves dissociation of π complex iii to give Pd(0), HCl, and nucleoside **7**. However, iii may be in equilibrium with both ii and iv. Intermediate iv, unlike ii, could dissociate with loss of Pd(0) to a stabilized carbocation, v, which would be expected to react with the most readily available source of nucleophile, methanol, to give nucleoside **8**. The reaction of ethylene with 5-(chloromercuri)uridine and Li_2PdCl_4 in MeOD previously established the occurrence of a palladium-mediated intramolecular hydride shift[4] as postulated here for the interconversion of intermediates ii and iv.

The trans stereochemistry of **7** is presumed on the basis of the 16-Hz coupling constant between the olefinic protons. In this and all other coupling reactions to olefins of structure CH_2=CHY, where Y is a group capable of conjugation, the isolated products have shown only trans stereochemistry.

Vinylogues of the nucleoside antibiotics toyocamycin (**2**) and sangivamycin (**3**) were synthesized by coupling acrylonitrile and acrylamide, respectively, to **4**. In meth-

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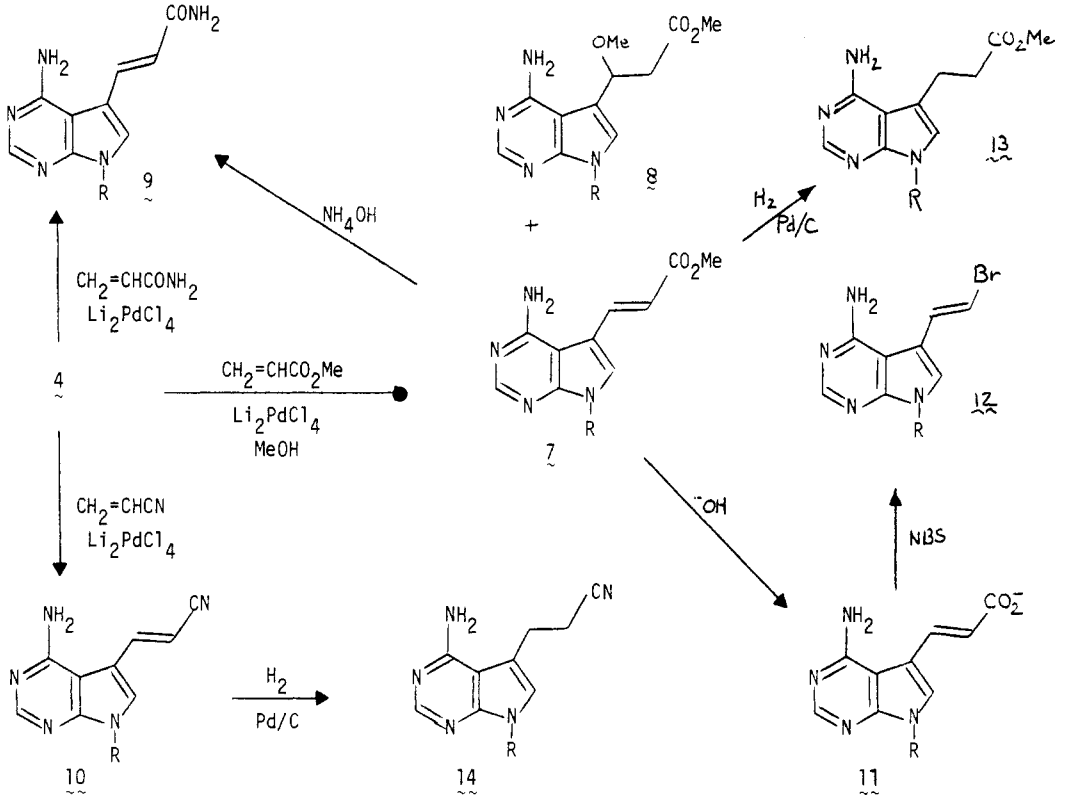
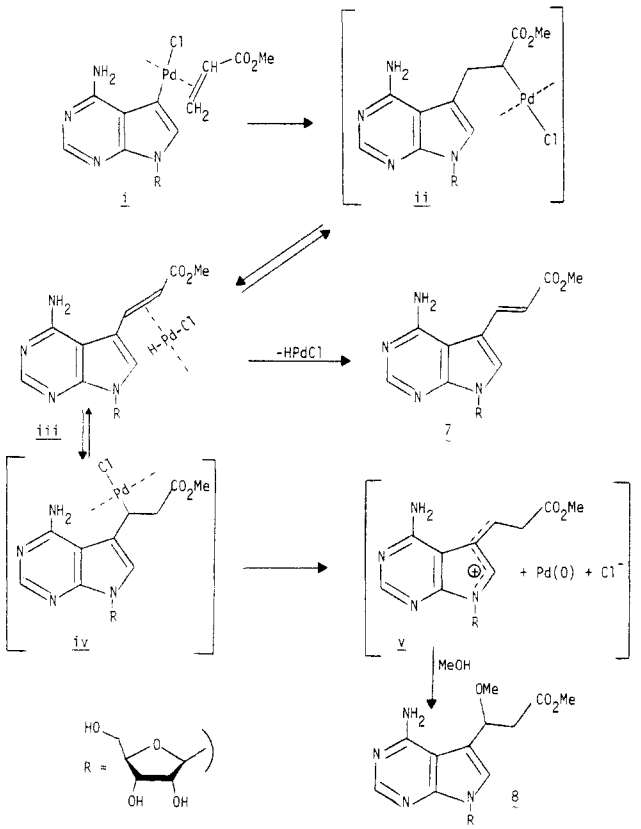
Scheme II



Scheme III



anol both reactions gave predominantly tubercidin, but when the reactions were carried out in 0.1 M Li_2PdCl_4–DMF, 5-(2-cyanoethenyl)tubercidin (**10**) was obtained in 22% yield and 5-(2-carboxamidoethenyl)tubercidin (**9**) in 7% yield. A far better route to **9** was ammonolysis of nucleoside **7** which proceeded in yields up to 95%. The side-chain double bonds of **7** and **10** could be reduced by H_2 over Pd/C without concomitant reduction of other functional groups to give nucleoside **13** and **14**, respectively (Scheme II). Nucleoside **7** has proved to be a versatile intermediate. Jones et al.[24] demonstrated that (*E*)-5-(2-carboxylvinyl)pyrimidine nucleosides could be decarboxylated and brominated by NBS in hot aqueous solution to give (*E*)-5-(2-bromovinyl)nucleosides in good yield. (*E*)-5-(2-Carboxyethenyl)tubercidin (**11**), prepared by hydroxide-catalyzed hydrolysis of **7**, did not react to give identifiable products with NBS in water but in DMF gave (*E*)-5-(2-bromoethenyl)tubercidin (**12**) in 26% yield. The 15-Hz coupling constant between the olefinic protons confirmed that the trans stereochemistry was retained.

Other reactions following the precedent established for 2'-deoxyuridine include coupling of **4** with ethylene, 3-chloro-1-butene, and styrene (Scheme IV). Mercuritubercidin **4** and ethylene with 0.1 M Li_2PdCl_4 in methanol gave 5-(1-methoxyethyl)tubercidin (**15**) in good yield (Scheme IV), presumably by a mechanism similar to that outlined in Scheme III for production of 5-[1-methoxy-2-(methoxycarbonyl)ethyl]tubercidin (**8**). The potential of nucleoside **15** as an intermediate for the introduction of other function groups to replace methoxy at C-1 was briefly investigated. In water at reflux, nucleoside **15** is transformed cleanly to 5-(1-hydroxyethyl)tubercidin (**16**). When the hydrolysis was attempted with an acid catalyst at room temperature, tubercidin (**1**) was produced. An acid-catalyzed retro-aldol type of reaction is very likely responsible (Scheme V). In this respect it is of interest to note the outcome of the reaction of mercuritubercidin **4** with ethylene and 0.1 M Na_2PdCl_4 in H_2O. Tubercidin (**1**) was the major product, while 5-(1-hydroxyethyl)-tubercidin was only a minor product. The HCl produced in the reaction may be catalyzing the retro-aldol reaction

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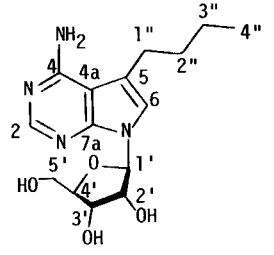
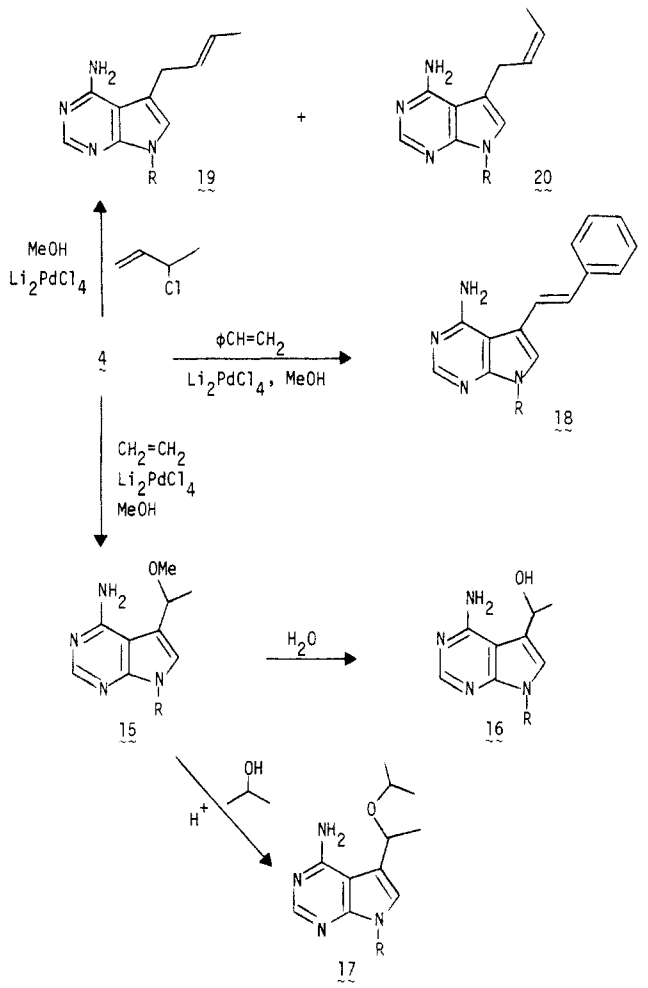
Table I. ^{13}C NMR Spectra[a]



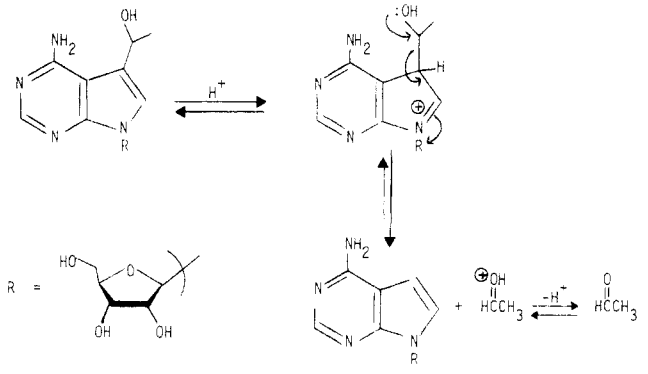
nucleoside	C-5 substituent	C-2	C-4	C-4a	C-5	C-6	C-7a	C-1′	C-2′	C-3′	C-4′	C-5′	C-1″	C-2″	C-3″	C-4″
1	H	151.5	157.5	103.1	99.5	122.3	149.9	87.6	73.7	70.8	85.1	61.9				
3	$CONH_2$	152.69	157.95		110.85	125.90	150.82	86.96	72.32	70.50	85.25	61.72	166.17			
5	CO_2Me	153.75	157.49	100.48	106.06	129.26	151.08	87.48	74.03	70.23	85.84	61.12	165.17		(OCH_3 51.80)	
6	CH_2OH	151.26	157.23	102.62	115.54	119.06	151.06	87.14	73.73	70.81	85.13	61.97	56.43			
7	$CH{=}CHCO_2Me$	151.50	157.38		110.49	123.65	151.10	86.97	73.78	70.29	85.03	61.49	136.39	115.06	166.27	(OCH_3 51.15)
8	$C(OMe)HCH_2CO_2Me$	152.23	154.84	102.05	115.40	122.17	151.06	87.60	73.95	71.08	85.41	62.0	73.95	42.37	174.96	(OCH_3 55.90, 52.73)
9	$CH{=}CHCONH_2$	151.57	157.27	100.79	111.47	122.78	150.90	86.96	73.85	70.57	85.20	61.66	130.64	121.11	167.16	
10	CH=CHCN	152.35	157.94	100.11	92.52	122.94	151.32	87.00	73.72	70.29	85.07	61.52	142.58	110.72	119.00	
11	$CH{=}CHCO_2H$	150.05	154.04	100.55	112.16	124.74	147.04	87.88	74.47	70.44	85.68	61.49	135.53	118.95	167.82	
12	CH=CHBr	151.01	156.86	100.12	111.22	119.74	150.88	86.83	73.55	70.26	84.95	61.49	128.58	104.93		
13	$CH_2CH_2CO_2Me$	150.48	156.67	101.24	112.62	118.69	149.82	86.17	72.63	69.74	84.00	60.93	20.45	33.86	171.94	(OCH_3 50.44)
14	CH_2CH_2CN	151.26	157.26	101.82	111.78	120.10	150.55	87.03	73.41	70.48	84.81	61.70	21.80	18.26		
15	$C(OMe)HCH_3$[a]	152.43	158.35	103.56	120.20	123.03	151.98	89.39	75.65	72.79	86.90	63.92	74.71	23.58	(OCH_3 56.88)	
16	$C(OH)HCH_3$	150.27	156.03	101.71	119.24	121.71	149.26	87.20	74.19	70.99	85.47	61.97	62.73	25.34		
18	CH=CHPh	151.40	157.61	100.88	113.83	120.26	150.79	86.90	73.64	70.47	84.98	61.67	unassigned			
19, 20	(*E*)- and (*Z*)-CH_2-$CH{=}CHCH_3$	151.73	157.74	102.92	114.32	120.53, 120.05	151.06	87.51	73.98	71.11	85.43	62.28	29.49, 24.33	130.53, 128.70	126.51, 125.90	18.22, 13.35
23	I	151.76	156.91			127.05	150.02	86.62	73.67	70.26	85.01	61.30				

[a] All spectra were run in Me_2SO-d_6 and are referenced to external Me_4Si with the exception of **15** which was run in D_2O.

Scheme IV



Scheme V



here as well. Since base inhibits the organopalladium coupling reaction, no attempt was made to prevent the acid-catalyzed reaction. Ethylene reacts with 5-(chloromercuri)-2′-deoxycytidine in methanolic 0.1 M Li_2PdCl_4 to give 5-(1-methoxyethyl)cytidine, whereas in DMF 5-vinyl-2′-deoxycytidine is obtained.[25] The reaction of **4** with ethylene in DMF gave a complex mixture of at least five products, none of which could be successfully isolated and identified.

The methoxy group at C-1 of **15** can be exchanged for other alkoxy groups under acid conditions; however, side reactions on the sugar have prevented us from obtaining well-defined, analytically pure products. In a refluxing mixture of 4% H_2SO_4 in 2-propanol, **15** was converted to **17** along with minor amounts of side products which could not be separated by chromatography on silica gel, Bio-gel P-2, or RP-8. Identification was based primarily on ^1H NMR. The spectrum was virtually identical with that for **15** except in place of the CH_3O resonance at 3.27 ppm there were two doublets centered at 1.13 ppm and integrating for six protons.

Styrene coupled with **4** in methanolic 0.1 M Li_2PdCl_4 to give (*E*)-5-(2-phenylethenyl)tubercidin (**18**) in 25% yield. Unlike (*E*)-5-(2-phenylethenyl)uridine,[4] **18** was not appreciably fluorescent. The trans stereochemistry was established by ^1H NMR at 360 MHz. At this high field the olefinic protons were clearly separated (7.01 and 7.54 ppm) and showed a 16.05-Hz coupling constant.

Like 2′-deoxyuridine,[26] mercuritubercidin **4** gave both *E* and *Z* isomers on coupling with 3-chloro-1-butene. The isomers, **19** and **20**, could not be separated by either TLC or high-pressure LC on an analytical C-18, reverse-phase column. However, their identity and relative yields were clearly established by a ^{13}C NMR spectrum of the mixture. The reaction between **4**, Li_2PdCl_4, and allyl chloride gave, as expected, 5-allyltubercidin (^1H NMR characterization); however, the low yields and complexity of the reaction mixture discouraged us from purifying and fully characterizing the product.

5-Mercuri-2′,3′-*O*-isopropylidenetubercidin was synthesized by mercuration of 2′,3′-*O*-isopropylidenetubercidin but could not be spectroscopically characterized because of its lack of solubility. Its tranformation to 5-(1-methoxyethyl)-2′,3′-*O*-isopropylidenetubercidin on reaction with ethylene and Li_2PdCl_4 in methanol confirmed the structure. The protecting group offered no advantage in either the ethylene reaction or in coupling to allyl chloride. The latter reaction still gave a complex mixture and low yields. We have done no other exploratory work with protecting groups in the tubercidin series. Protection of the amino function could be useful in preventing formation of insoluble mercury complexes and potentially less reactive organopalladium intermediates. However, our experience with cytidine revealed unanticipated problems. Reaction of *N*-anisoylcytidine with mercuric acetate resulted in loss of the protecting group and isolation of 5-mercuricytidine. A counter approach, acylation of mercuricytidine by acetic anhydride, gave only recovered starting material.

Finally, the halogenation of mercuritubercidin was investigated in the interest of developing a short route to the 5-chloro-, 5-bromo-, and 5-iodotubercidins. All exhibit significant biological activity, but, in particular, 5-bromotubercidin (**22**) was demonstrated to be an in vivo reversible inhibitor of RNA synthesis[27] and 5-iodotubercidin (**23**) a potent inhibitor of adenosine kinase.[28] The halogenation of 5-mercuritubercidin (**4**) was not anticipated to be a problem in light of the successful halogenation of 5-mercuripyrimidine nucleotides.[29] Iodination by I_2 in methanol–water, DMF, or HMPA proceeded smoothly, but purification of the product was difficult because of the insolubility of **23** in water (neutral, acidic, or basic) and organic solvents, with the exception of HMPA and methanol (sparingly soluble). Elimination of all traces of mercuric iodide was especially tedious. Column chromatography on silica gel with elution with

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(29) Dale, R. M. K.; Martin, E.; Livingston, D. C.; Ward, D. C. *Biochemistry* **1975**, *14*, 2447–57.

methanol–chloroform resulted in substantial loss of material, but the purity was then sufficient for recrystallization from methanol. A minor product which separated but could never be purified was assigned the structure of 5,6-diiodotubercidin on the basis of the resemblance of its ^{1}H NMR spectrum to that for 5,6-dibromotubercidin.[30] Approximately 10% diiodination was anticipated on the basis of the structure of 4. Bromination of 4 with either Br_2, NBS, or $CuBr_2$ in methanol, water, or DMF gave complex mixtures of products of which 5-bromotubercidin was a major (but in overall low yield) constituent. Further investigation of this reaction was dropped when it was discovered that 5-bromotubercidin and 5-chlorotubercidin could be obtained in good yield by the direct reaction of tubercidin with NBS and NCS, respectively.[30]

Conclusion

5-Mercuritubercidin (4), although not structurally well-defined, is a useful intermediate for synthesis of C-5-substituted tubercidin derivatives. Organopalladium intermediates derived from 4 can be formed and coupled to olefins or carbon monoxide under exceedingly mild conditions. Protecting groups for either the sugar hydroxyl groups or N-4 are unnecessary. Although in many instances the yields are low, no other methodology offers as direct an entry into C-5-substituted tubercidins.

Experimental Section

Proton magnetic resonance spectra were taken on either a Varian EM360 60-Mz instrument or a Fourier transform NMR JEOL Model PS100. Sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate (TSP) was employed as the internal standard for spectra run in D_2O or Me_2SO-d_6. ^{13}C NMR spectra were obtained on the latter instrument. Infrared spectra were obtained on a Beckman IR-8 in solid KBr with a polystyrene standard. Ultraviolet spectra were measured on either a Cary 15 or Cary 17 spectrometer. Melting points were taken on a Büchi 510 melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories or the Microanalytical Laboratory of the University of California at Berkeley. Column chromatography was done on Bio-Gel P2 and E. Merck silica gel 60. Unless specified otherwise, column chromatography on silica gel was accomplished by using a step gradient from 10% MeOH–$CHCl_3$ to 40% MeOH–$CHCl_3$. The percentage of methanol was increased by 5% every 100 mL of solvent mixture (200 g of silica gel/100 mL of solvent mixture). Analytical thin-layer chromatography (TLC) was carried out on E. Merck, precoated, silica gel F-254 (0.25 mm), plastic-backed TLC sheets cut to 30 × 110 mm. The sheets were developed in the specified solvent systems in 12-cm-high, wide-mouth jars lined with filter paper. The solvent systems were as follows: A, MeOH–$CHCl_3$ (1:3 v/v); B, MeCN–*n*-BuOH–0.1 M NH_4OAc–concentrated NH_4OH (10:60:20:10 v/v); C, MeOH–EtOAc (3:2 v/v). All solvents and reagents were reagent grade. Tubercidin was purchased from the Upjohn Co. Fine Chemicals Division. Water was deionized and then distilled through glass. Coupling reactions with ethylene and hydrogenations were carried out in Parr bottles by using an apparatus similar to that described by Barefield.[31] The apparatus was modified from the one described by the addition of a separate permanent connection adapted for easy exchange of lecture bottles.

For purposes of reference, tubercidin has the following properties: mp 247 °C dec; UV λ_{max} 272 (ϵ 12 200) in 0.01 M HCl, 270 (12 100) in 0.01 M NaOH; IR (KBr) 3200 (br), 1600 (br), 1450, 1362, 1260, 1140, 1051, 1012, 912, 878 cm^{-1}; TLC (solvent system/R_f value) A/0.28, B/0.43, C/0.54; ^{1}H NMR (Me_2SO-d_6) δ 8.18 (1 H, s, H2), 7.45 (1 H, d, J = 4 Hz, H6), 7.17 (2 H, s, NH_2), 6.70 (1 H, d, J = 4 Hz, H5), 6.11 (1 H, d, J = 6 Hz, H1′), 4.55 (1 H, H4′), 4.1 (2 H, H2′ and H3′), 3.6 (2 H, m, H5′).

5-(Methoxycarbonyl)tubercidin (5). To a 250-mL Parr bottle were added 5-mercuritubercidin (525 mg, 0.946 mmol) and 20 mL of a methanolic 0.1 M Li_2PdCl_4 solution (2 mmol). The mixture was stirred under 35 psi of carbon monoxide for 3 days at 25 °C. The reaction mixture was filtered, saturated with hydrogen sulfide, and refiltered. Neutralization with concentrated NH_4OH, evaporation onto 3 g of silica gel, and chromatography on 200 g of silica gel with a chloroform–methanol gradient gave 5 as white crystals: 77 mg (0.23 mmol, 24%); mp 214.5–216 °C (lit.[16] mp 216–218 °C). The product exhibited a single component on TLC (silica gel, system A) and high-pressure LC (C-18 reverse phase; 0.01 M $NH_4H_2PO_4$–acetonitrile, 85:15 v/v); ^{1}H NMR (Me_2SO-d_6) δ 8.31 (s, 1 H), 8.17 (s, 1 H), 6.12 (d, 1 H, J = 6 Hz), 4.44 (m, 1 H), 4.0 (br m, 2 H), 3.83 (s, 3 H), 3.62 (m, 2 H); UV λ_{max} (MeOH) 276 nm, 229.

Anal. Calcd for $C_{13}H_{16}N_4O_6$: C, 48.15; H, 4.97; N, 17.28. Found: C, 48.02; H, 5.10; N, 17.10.

5-Carboxamidotubercidin (Sangivamycin, 3). 5-(Methoxycarbonyl)tubercidin (5; 0.092 g, 0.284 mmol) and ammonium chloride (0.82 g) were dissolved in concentrated ammonium hydroxide (15 mL) with warming. Once the 5 was completely dissolved, the mixture was cooled and allowed to stir at room temperature for 7 h. Evaporation to dryness in vacuo gave a white solid. Chromatography on silica gel with elution with a gradient of 15–40% methanol–chloroform gave 3: 52 mg (59%); R_f 0.15 (system A). The ^{13}C NMR spectrum was virtually identical with that reported for sangivamycin by Chenon et al.[21]

5-(Hydroxymethyl)tubercidin (6). 5-(Methoxycarbonyl)-tubercidin (1.246 g, 3.84 mmol) in 70 mL of dry THF was combined with $LiBH_4$ (0.836 g, 38 mmol) and refluxed under an argon atmosphere for 20 h. The reaction mixture was then evaporated four times with 10-mL portions of methanol containing about 5% HCl. The reaction mass was then taken up in methanol, neutralized with concentrated NH_4OH, and evaporated with 7 g of silica gel. Chromatography on 300 g of silica gel with a chloroform–methanol gradient afforded, after recrystallization from methanol, 6 as white crystals: 518 mg (1.74 mmol, 45%); mp 219–220.5 °C; high pressure LC (C-18 reverse phase; 0.01 M $NH_4H_2PO_4$–acetonitrile, 92:8 v/v) and TLC (silica gel, system A) indicated a pure product; ^{1}H NMR (Me_2SO-d_6) δ 8.13 (s, 1 H), 7.32 (s, 1 H), 6.05 (d, 1 H, J = 6 Hz), 4.63 (s, 2 H), 4.47 (m, 1 H), 4.12 (m, 1 H), 3.93 (m, 1 H), 3.59 (m, 2 H); UV (MeOH) λ_{max} 270 nm.

Anal. Calcd for $C_{12}H_{16}N_4O_5$: C, 48.65; H, 5.44; N, 18.91. Found: C, 48.83; H, 5.54; N, 18.83.

5-[2-(Carbomethoxy)ethenyl]tubercidin (7) and 5-[1-Methoxy-2-(carbomethoxy)ethyl]tubercidin (8). 5-Mercuritubercidin (0.5013 g, 1 mmol) and methyl acrylate (0.902 mL, 10.0 mmol) were dissolved in 0.1 M Li_2PdCl_4–MeOH (20.0 mL, 2.00 mmol) and stirred for 20 h. The mixture was treated with H_2S and then gravity filtered to remove metal sulfides. The filtrate was evaporated to dryness and chromatographed on a silica gel column (100 g, 2-cm diameter) with MeOH–$CHCl_3$ gradient. Fractions containing a product with R_f 0.46 (TLC system A) were pooled; the resulting solution was evaporated to dryness, and then the residue was chromatographed on a column of Bio-Gel P2 (100 g, 2-cm diameter) with H_2O as elutant. Fractions containing the product with R_f 0.46 (TLC system A) were pooled and lyophilized to give a light yellow solid. Drying overnight in vacuo over P_2O_5 gave 7: 0.2013 g (0.5746 mmol, 57% yield); mp 120 °C dec; TLC (solvent system/R_f value) A/0.45, B/0.40, C/0.56; ^{1}H NMR (Me_2SO-d_6) δ 8.20 (s, 1 H, H2 or H6), 8.18 (s, 1 H, H2 or H6), 8.02 (d, 1 H, J = 16 Hz, H1″), 6.95 (s, 2 H, NH_2), 6.45 (d, 1 H, J = 16 Hz, H2″), 6.12 (d, 1 H, J = 6 Hz, H-1′), 4.45 (m, 1 H, H4′), 4.17–3.98 (m, 2 H, H-2′, H-3′), 3.76 (s, 3 H, OCH_3), 3.65 (m, 2 H, H5′), UV (pH 1.5, aqueous HCl) λ_{max} 308 nm (ϵ 13 460), λ_{min} 277 (10 170), λ_{max} 251 (13 970), λ_{min} 237 (13 470); UV (pH 6.4, water) λ_{max} 321 (11 610), λ_{min} 299 (10 390), λ_{max} 270 (11 840), λ_{min} 238 (8240); UV (pH 12.6, aqueous NaOH) λ_{max} 296 (12 900), λ_{min} 275 (10 810), λ_{max} 267 (11 210); IR (KBr) 3340 (br), 1620, 1585, 1440, 1300, 1190, 1080 cm^{-1}.

(30) Bergstrom, D. E.; Brattesani, A. J. *Nucleic Acids Res.* **1980**, *8*, 6213–9.

(31) Barefield, E. Kent *J. Chem. Educ.* **1973**, *50*, 697.

(32) **Note Added in Proof.** Watanabe and Ueda have recently demonstrated that a carbon unit can be introduced into the C-5 position by a Mannich reaction on 2′,3′,5′-tri-*O*-acetyltubercidin. Watanabe, S., Ueda, T. *Nucleic Acids Res., Symp. Ser. No. 8* **1980**, S21–6.

Anal. Calcd for $C_{15}H_{18}N_4O_6 \cdot {}^3/_4H_2O$: C, 49.52; H, 5.40; N, 15.40. Found: C, 49.57; H, 5.31; N, 15.40.

The 1″-methoxy adduct side product, **8**, formed in 9% yield in this specific reaction. This compound is very hygroscopic: ^{1}H NMR (D_2O) δ 8.36 (s, 1 H, H2), 7.67 (s, 1 H, H6), 6.24 (d, 1 H, J = 6 Hz, H1′), 5.3–3.8 (m, 6 H, ribosyl and H1″), 3.73 (s, 3 H, CO_2CH_3), 3.37 (s, 3 H, OCH_3), 2.90 (m, 2 H, H2″); TLC (solvent system/R_f value) A/0.53, B/0.47.

5-(2-Carboxamidoethenyl)tubercidin (9). Method A. 5-Mercuritubercidin (0.5013 g, 1.0 mmol) was stirred with acrylamide (0.710 g, 10.00 mmol) in 0.1 M Li_2PdCl_4–DMF (14 mL, 1.4 mmol) for 2 days and diluted with 14 mL of methanol, and the resulting solution was saturated with H_2S gas. The mixture was gravity filtered to remove metal sulfides, and the filtrate was evaporated to dryness. The residue was chromatographed on a silica gel column (100 g, 2-cm diameter) with a MeOH–$CHCl_3$ gradient, and fractions containing a product with R_f 0.33 (TLC system B) were pooled, evaporated to dryness, and rechromatographed on a column of Bio-Gel P2 (100 g, 2.5-cm diameter) with water as elutant. Fractions containing one product with R_f 0.33 (TLC system B) were pooled and concentrated to allow crystallization of a white product. The solid was collected by gravity filtration and then dried 24 h in vacuo over P_2O_5 to give pure **9**: 0.0234 g (0.070 mmol, 7% yield); mp 220 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 8.17 (s, 1 H, H2), 7.98 (s, 1 H, H6), 7.71 (d, 1 H, J = 16 Hz, H1″), 6.89 (s, 2 H, NH_2), 6.36 (d, 1 H, J = 16 Hz, H2″), 6.12 (d, 1 H, J = 6 Hz, H1′), 4.47 (m, 1 H, H4′), 4.05 (m, 2 H, H3′, H2′), 3.67 (m, 2 H, H5′); IR (KBr) 3290 (br), 1618, 1460, 1300, 1060 cm^{-1}; UV (pH 1.5, aqueous HCl) λ_{max} 306 (15 690), λ_{min} 275 (10 840), λ_{max} 246 (17 820), λ_{min} 228 (14 140); UV (pH 5.9, H_2O), λ_{max} 310 (14 120), λ_{min} 279 (11 470), λ_{max} 267 (12 520), λ_{min} 236 (9452); UV (pH 12.6, aqeuous NaOH) λ_{max} 312 (14 330), λ_{min} 279 (11 290), λ_{max} 268 (12 440), λ_{min} 238 (9653); TLC (solvent system/R_f value) A/0.08, B/0.33, C/0.38.

Anal. Calcd for $C_{14}H_{17}N_5O_5 \cdot {}^1/_2H_2O$: C, 48.84; H, 5.27; N, 20.34. Found: C, 48.61; H, 5.07; N, 20.09.

Method B. 5-[2-(Carbomethoxy)ethenyl]tubercidin (**7**; 0.029 g, 0.083 mmol) and NH_4Cl (0.021 g) were stirred in concentrated NH_4OH (4 mL) for 7 h at room temperature. After 4 h of reaction a white precipitate appeared in the viscous solution. After 7 h the crop of crystals was collected by filtration, washed, and dried overnight in vacuo over P_2O_5 to give **9** (0.0261 g, 0.078 mmol, 95% yield). This product was compared with **9** from the coupling run by TLC (four solvent systems), UV, IR, and ^{1}H NMR spectra, and melting point.

5-(2-Cyanoethenyl)tubercidin (10). 5-Mercuritubercidin (1.0026 g, 2.000 mmol) was stirred with acrylonitrile (1.33 mL, 20.0 mmol) and 0.1 M Li_2PdCl_4–DMF (40.0 mL, 4.00 mmol) for 8 days and diluted with 40 mL of methanol, and the resulting solution was saturated with H_2S. The mixture was neutralized and gravity filtered to remove the metal sulfides, and then the filtrate was evaporated to dryness. The residue was chromatographed on a silica gel column (150 g, 2.5-cm diameter) with a MeOH–$CHCl_3$ gradient, and all fractions containing a product with R_f 0.34 (TLC system A) were combined. This pool was evaporated to dryness and then chromatographed on a column of Bio-Gel P2 (100 g, 2.3-cm diameter) with water as the elutant. Fractions showing one product with R_f 0.34 (system A) were pooled, and the resulting solution concentrated to allow crystallization of a white product, which was eventually collected by filtration. The solid was dried overnight in vacuo over P_2O_5 to give pure **10**: 0.1356 g (0.428 mmol, 22% yield); mp 168 °C dec; TLC (solvent system/R_f value) A/0.34, B/0.48, C/0.68; ^{1}H NMR (Me_2SO-d_6) δ 8.20 (s, 1 H, H2 or H6), 8.17 (s, 1 H, H2 or H6), 8.14 (d, 1 H, J = 16.5 Hz, CH=CHCN), 7.13 (s, 2 H, NH_2), 6.17 (d, 1 H, J = 16.5 Hz, CH=CHCN), 6.12 (d, 1 H, J = 5 Hz, H1′), 4.44 (m, 1 H, H4′), 4.08 (m, 2 H, H2′ and H3′), 3.65 (m, 2 H, H5′); IR (KBr) 3280 (br), 2230, 1614, 1575, 1444, 1310, 1203, 1050 cm^{-1}; UV (pH 1.2, aqueous HCl) λ_{max} 311 (ϵ 16 810), λ_{min} 280 (10 410), λ_{max} 225 (19 430), λ_{min} 231 (10 530); UV (MeOH, "neutral") λ_{max} 323 (14 790), λ_{min} 285 (10 190), λ_{max} 268 (15 540), λ_{min} 236 (6370); UV (pH 12.5, aqueous NaOH) λ_{max} 319 (14 010), λ_{min} 286 (11 610), λ_{max} 268 (15 500), λ_{min} 238 (8493).

Anal. Calcd for $C_{14}H_{14}N_4O_4 \cdot {}^1/_2H_2O$: C, 51.53; H, 4.94; N, 21.46. Found: C, 51.53; H, 5.08; N, 21.51.

(*E*)-5-(2-Carboxyethenyl)tubercidin (11). To 20 mL of 0.5 M NaOH solution was added 5-[2-(methoxycarbonyl)ethenyl]-tubercidin (**7**; 1.227 g, 3.51 mmol). After 3 h at room temperature, the reaction mixture was acidified with 15% HCl to give, after being filtered and dried at high vacuum, **11** as a white powder: 1.030 g (3.06 mmol, 87%); mp >300 °C; high-pressure LC (C-18 reverse phase; 0.01 M $NH_4H_2PO_4$–acetonitrile, 95.5 v/v) and TLC (silica gel, system A) showed a single component; ^{1}H NMR (Me_2SO-d_6) δ 8.38 (s, 1 H), 8.32 (s, 1 H), 7.98 (d, 1 H, J = 16 Hz), 6.46 (d, 1 H, J = 16 Hz), 6.20 (d, 1 H, J = 6 Hz), 4.47 (m, 1 H), 4.18 (m, 1 H), 4.00 (m, 1 H), 3.71 (m, 2 H); UV (MeOH) λ_{max} 313 nm, 261.

Anal. Calcd for $C_{14}H_{16}N_4O_6 \cdot H_2O$: C, 47.45; H, 5.12; N, 15.82. Found: C, 47.09; H, 4.94; N, 15.67.

(*E*)-5-(2-Bromoethenyl)tubercidin (12). A mixture of 5-(2-carboxyethenyl)tubercidin (**11**; 170 mg, 0.50 mmol) and potassium acetate (100 mg, 1.0 mmol) in 7 mL of dry DMF was heated on the steam bath to give a cloudy solution. The stirred mixture was cooled to room temperature, *N*-bromosuccinimide (90 mg, 0.50 mmol) in 1 mL of dry DMF was added dropwise, and the mixture was then stirred for 10 min. The reaction mixture was evaporated, taken up in methanol, evaporated with 3 g of silica gel, and chromatographed in a 2-cm-diameter column of 200 g of silica gel, giving, after recrystallization from methanol, **12** as light orange crystals: 50 mg (0.13 mmol, 26%); mp 164.5–167 °C; high-pressure LC (C-18 reverse phase; $NH_4H_2PO_4$–acetonitrile, 83:17 v/v) and TLC (silica gel, system A) showed a single component; ^{1}H NMR (Me_2SO-d_6) δ 8.38 (s, 1 H), 7.96 (s, 1 H), 7.87 (d, 1 H, J = 15 Hz), 7.09 (d, 1 H, J = 15 Hz), 6.26 (d, 1 H, J = 6 Hz), 4.58 (m, 1 H), 4.28 (m, 1 H), 4.06 (m, 1 H), 3.78 (m, 2 H); UV (MeOH) λ_{max} 282 nm, 243.

Anal. Calcd for $C_{13}H_{15}BrN_4O_4$: C, 42.06; H, 4.07; Br, 21.53; N, 15.09. Found: C, 42.04; H, 4.17; Br, 21.56; N, 15.07.

5-[2-(Carbomethoxy)ethyl]tubercidin (13). 5-[2-(Carbomethoxy)ethenyl]tubercidin (**7**; 0.0360 g, 0.103 mmol) and 10% Pd/C catalyst (0.011 g, 10 mol % Pd/nucleoside) were stirred in methanol (20 mL) under 30 psig of H_2 in a 200-mL Parr flask for 4 h. The Pd/C was removed from the mixture by gravity filtration, and then the filtrate was evaporated to leave **13** as a cream-white solid: 0.036 g (quantitative); mp 93 °C dec; ^{1}H NMR (D_2O) δ 7.80 (s, 1 H, H2), 6.87 (s, 1 H, H6), 5.98 (d, 1 H, J = 5.5 Hz, H1′), 4.7–4.1 (complex m, 3 H, H4′, H3′, H2′), 3.9 (m, 2 H, H5′), 3.69 (s, 3 H, OCH_3), 2.53 (br s, 4 H, H1″, H2″); UV (H_2O) λ_{max} 277, λ_{min} 248; TLC (solvent systems/R_f value) A/0.42, B/0.46, C/0.54.

Anal. Calcd for $C_{15}H_{20}N_4O_6$: C, 51.13; H, 5.72; N, 15.90. Found: C, 50.97; H, 5.65; N, 15.76.

5-(2-Cyanoethyl)tubercidin (14). 5-(2-Cyanoethenyl)-tubercidin (800 mg, 3.78 mmol) was stirred at room temperature under 30 psig of H_2 in 100 mL of MeOH with 80 mg of 10% Pd/C for 6 h. Chromatography of the crude product, obtained from the filtrate after filtration and evaporation, on silica gel with elution with MeOH/$CHCl_3$ gave 5-(2-cyanoethyl)tubercidin: 610 mg (76%); mp 223–224.5 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.75 (t, 2 H, J = 7 Hz), 3.13 (t, 2 H, J = 7 Hz), 3.59 (m, 4 H), 3.90 (m, 1 H), 4.10 (m, 1 H), 4.40 (m, 1 H), 5.50 (m, 2 H), 6.01 (d, 1 H, J = 6 Hz), 6.76 (s, 1 H), 7.27 (s, 1 H), 8.07 (s, 1 H); TLC R_f 0.41 (system B); UV (H_2O) λ_{max} 276 nm (pH 5), 278 (pH 1.5), 274 (pH 12).

Anal. Calcd for $C_{14}H_{17}N_5O_4$: C, 52.66; H, 5.36; N, 21.93. Found: C, 52.43; H, 5.44; N, 21.71.

5-(1-Methoxyethyl)tubercidin (15). 5-Mercuritubercidin (1.767 g, 3.53 mmol) was suspended in a solution of 0.1 M Li_2PdCl_4–MeOH (70 mL, 7.0 mmol) in a 500-mL Parr bottle, and the mixture was stirred under 30 psig of ethylene for 24 h. A black precipitate appeared during the course of the reaction. The mixture was gravity filtered and the precipitate washed with 70 mL of methanol. H_2S was bubbled into the combined filtrates for 1 min and the solution immediately refiltered, the black metal sulfides then being washed with 50 mL of methanol. The filtrate was evaporated to a yellow oil, which was dissolved in water and neutralized with NH_4OH. The solution was evaporated to dryness, and the residue chromatographed on a silica gel column (150 g, 2.5-cm diameter) with a MeOH–$CHCl_3$ gradient. The residue from

evaporation of fractions containing a product with an R_f of 0.50 (TLC system A) was rechromatographed on a Bio-Gel P2 column (150 g, 2.3-cm diameter) with H_2O as elutant. Fractions showing a single spot on TLC were combined and lyophilized to a fluffy white solid. Drying 24 h over P_2O_5 in vacuo gave pure **15**: 0.837 g (2.58 mmol, 73% yield); mp 90 °C dec; ^1H NMR (D_2O) δ 8.15 (s, 1 H, H-2), 7.36 (s, 1 H, H-6), 6.19 (d, 1 H, J = 6 Hz, H-1′), 4.9–4.2 (m, 4 H, H-4′, H-3′, H-2′, and H-1″), 3.88 (m, 2 H, H-5′), 3.27 (s, 3 H, OCH_3), 1.48 (d, 3 H, J = 6 Hz, H-2″); UV (pH 1.9, aqueous HCl) λ_{max} 276 nm (ϵ 9420), λ_{min} 249 (4410); UV (pH 6.7, H_2O) λ_{max} 272 (10 100), λ_{min} 242 (3660); UV (pH 13.0, aqueous NaOH) λ_{max} 272 (10 100), λ_{min} 242 (3810); IR (KBr) 3360 (br), 1630, 1585, 1470, 1298, 1213, 1085 cm^{-1}; TLC (solvent system/R_f value) A/0.50, B/0.49, C/0.45.

Anal. Calcd for $C_{14}H_{20}N_4O_5 \cdot {}^1/_2H_2O$: C, 50.44; H, 6.35; N, 16.81. Found: C, 50.88; H, 6.19; N, 16.76.

5-(1-Hydroxyethyl)tubercidin (16). 5-(1-Methoxyethyl)-tubercidin (**15**, 0.2021 g, 0.6230 mmol) was refluxed in pH 7 water (25 mL) for 12 h. The solution was evaporated to dryness, and 25 mL of water was added, the reflux then being continued for 3 more days. At this time TLC indicated that only one product had formed (solvent system/R_f value): A/0.28, B/0.43. The solution was lyophilized to a white solid, **16**: 0.1876 g (0.6043 mmol, 97% yield); ^1H NMR (D_2O) δ 7.94 (s, 1 H, H2), 7.25 (s, 1 H, H6), 6.17 (d, 1 H, J = 5.5 Hz, H1′), 4.9–4.2 (m, 4 H, H4′, H3′, H2′, H1″), 3.96 (s, 2 H, H5′), 1.53 d, 3 H, J = 6 Hz, H2″).

Anal. Calcd for $C_{13}H_{18}N_4O_5 \cdot {}^1/_2H_2O$: C, 48.89; H, 6.00; N, 17.55. Found: C, 48.94; H, 5.82; N, 17.77.

5-(2-Phenylethenyl)tubercidin (18). 5-Mercuritubercidin (**4**; 5.25 g, 10.5 mmol) was combined with styrene (5.7 mL, 50 mmol) and 200 mL of methanolic 0.1 M Li_2PdCl_4 solution (20 mmol) and refluxed with stirring for 18 h. The reaction mixture was then filtered, saturated with hydrogen sulfide, refiltered, and neutralized with concentrated NH_4OH. The solution was evaporated with 10 g of silica gel and chromatographed on a 4-cm-diameter column containing 300 g of silica gel with elution with a chloroform–methanol gradient. The chromatographic fractions containing the product were evaporated to a yellow oil, dissolved in 20 mL of methanol, and cooled overnight at 0 °C to yield 830 mg of yellow crystalline product. The mother liquor was reduced and yielded a second crop of 145 mg of product: total yield 975 mg (2.65 mmol, 25.3%); mp 220.5–224 °C; high-pressure LC (C-18 reverse phase; 0.01 M $NH_4H_2PO_4$–acetonitrile, 7:3 v/v) and TLC (silica gel, system A) indicated a homogeneous product; ^1H NMR (Me_2SO-d_6) (100 MHz) δ 8.12 (s, 1 H), 7.90 (s, 1 H), 7.72–7.22 (m, 5 H), 7.57 (d, 1 H, J = 16.5 Hz), 7.04 (d, 1 H, J = 16.5 Hz), 6.12 (d, 1 H, J = 6 Hz), 4.47 (m, 1 H), 4.14 (m, 1 H), 3.95 (m, 1 H), 3.64 (m, 2 H); ^1H NMR (Me_2SO-d_6, 360 MHz) δ 8.08 (s, 1 H, H-2), 7.85 (s, 1 H, H-6), 7.67 (d, 2 H, J = 7.45 Hz, *o*-H), 7.36 (unsym, 2 H, *m*-H), 7.23 (t, 1 H, J = 7.32 Hz, *p*-H), 7.54 (d, 1 H, J = 16.06 Hz, H-1″ [Table I]), 7.01 (d, 1 H, J = 16.04 Hz, H-2″), 6.08 (d, 1 H, J = 6.2 Hz), 4.44 (m, 1 H, H-2′), 4.12 (m, 1 H, H-3′), 3.91 (m, 1 H, H-4′), 3.53–3.70 (m, 2 H, H-5′); UV (MeOH) λ_{max} 310 nm, 268.

Anal. Calcd for $C_{19}H_{19}N_4O_2$: C, 62.12; H, 5.21; N, 15.25. Found: C, 61.85; H, 5.42; N, 15.09.

(*E*)- and (*Z*)-5-(2-Buten-1-yl)tubercidins (19 and 20). 5-Mercuritubercidin (0.525 g, 1.0 mmol), 3-chloro-1-butene (1.01 mL, 10 mmol), and a methanolic 0.1 M $LiPdCl_4$ solution (10 mL, 1.0 mmol) were combined and stirred 48 h at room temperature. The reaction mixture was saturated with H_2S, filtered, neutralized with concentrated NH_4OH, and evaporated with 5 g of silica gel. Chromatography on 200 g of silica gel with elution with a chloroform–methanol gradient gave, after recrystallization from methanol, **19** and **20** as white crystals: 65 mg (0.20 mmol, 20%); mp 187.5–190 °C; high-pressure LC (C-18 reverse phase; 0.01 M $NH_4H_2PO_4$, 85:15 v/v) and TLC (silica gel, system A) showed a single component; ^1H NMR (Me_2SO-d_6) δ 8.11 (s, 1 H), 7.18 (s, 1 H), 6.05 (d, 2 H, J = 6 Hz), 5.65 (narrow m, 2 H), 4.49 (m, 1 H), 4.15 (m, 2 H), 3.68 (narrow m, 2 H), 3.49 (narrow m, 2 H), 1.69 (narrow m, 3 H); the ratio of *E* to *Z* isomer was estimated to be 2:1 on the basis of the ^{13}C resonances; UV (MeOH) λ_{max} 275 nm.

Anal. Calcd for $C_{15}H_{20}N_4O_2$: C, 56.24; H, 6.29; N, 17.49. Found: C, 56.52; H, 6.36; N, 17.62.

5-Iodotubercidin (23). 5-Mercuritubercidin (**4**; 1.575 g, 3.0 mmol) and iodine (1.53 g) were dissolved with stirring in 50 mL of DMF. After 18 h the DMF was removed by lyophilization and the brown oil chromatograhed on silica gel (100 g) with elution with 16% MeOH/$CHCl_3$. Fractions of 15 mL were collected. Fractions 8–45 were combined and evaporated to give a mixture of **23** and mercuric iodide. Most of the mercuric iodide could be eliminated by washing the solid first with acetone and then with methanol. Rechromatography on silica gel gave **23** (0.5486 g, 47%). Analytically pure 5-iodotubercidin (mp 190–191 °C dec) could be obtained by recrystallization from methanol: ^1H NMR (Me_2SO-d_6–D_2O) δ 3.57 (narrow m, 2 H), 3.91 (m, 1 H), 4.09 (m, 1 H), 4.36 (m, 1 H), 6.03 (d, 1 H, J = 6.3 Hz), 7.68 (s, 1 H), 8.11 (s, 1 H); UV (MeOH) λ_{max} 282 nm (ϵ 9030).

Anal. Calcd for $C_{11}H_{13}N_4O_4I$: C, 33.69; H, 3.34; N, 14.29. Found: C, 33.85; H, 3.40; N, 14.18.

Acknowledgment. The authors express their appreciation for help in synthesis to Thomas Kemp, Christopher Haines, and Mary Powers, and to Paul Bruins for running the ^{13}C NMR spectra. This work was supported by the U.S. Army Medical Research and Development Command under Research Contract DAMD-17-79-C-8014 and by Grant No. CA21493 awarded by the National Cancer Institute, whom we gratefully acknowledge.

Registry No. **3**, 18417-89-5; **4**, 76319-78-3; **5**, 18440-68-1; **6**, 49558-38-5; **7**, 76319-79-4; **8**, 76319-80-7; **9**, 76319-81-8; **10**, 76319-82-9; **11**, 76319-83-0; **12**, 76319-84-1; **13**, 76319-85-2; **14**, 76319-86-3; **15**, 76319-87-4; **16**, 76319-88-5; **18**, 76319-89-6; **19**, 76319-90-9; **20**, 76319-91-0; **23**, 24386-93-4; 5-(acetoxymercuri)tubercidin, 76319-92-1; methyl acrylate, 96-33-3; acrylamide, 79-06-1; acrylonitrile, 107-13-1; styrene, 100-42-5; 3-chloro-1-butene, 563-52-0; tubercidin, 69-33-0.