

### Thiourea Derivatives of 2-Aminooxazoles Showing Antibacterial and Antifungal Activity

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Compounds of simple structure prepared by inexpensive procedures, possessing antibacterial and antifungal activity, have potential use in medicine, in veterinary work, and in agriculture. This paper records the discovery of a series of thioureas, prepared by simple chemical reactions, which have interesting activity of this type.

The potential biological activity of oxazoles has been under investigation in this laboratory and an earlier paper reported on amide and urea derivatives of 2-aminooxazole having some degree of antiinflammatory activity.<sup>1</sup> As a sequel some analogous thioureas were synthesized and found to have quite widespread activity against bacteria and especially fungi. A fuller series of thioureas has now been prepared in order to establish the scope and structural requirements of this activity. On the basis of the *in vitro* results, the best compounds were chosen for evaluation as agricultural fungicides. Greenhouse tests showed activity against common plant foliage and plant soil diseases.

**Chemistry.** Starting materials for the investigation, prepared by reported procedures, were 2-aminooxazole<sup>2</sup> and its 4-methyl,<sup>1</sup> 4-trifluoromethyl,<sup>1</sup> 4,5-dimethyl, and 4,5-diphenyl derivatives.<sup>3</sup> The thioureas listed in Table I were prepared by the reaction of an aminooxazole with the appropriate isothiocyanate in an anhydrous solvent.



The solvents examined for this reaction were pyridine, dioxane, toluene, and benzene. Pyridine was the best general solvent from consideration of yield, reaction time, and cleanness of product, with toluene a second choice. However, where R = allyl, excessive polymerization and tar formation were observed in these solvents, but the reaction was conducted successfully in benzene. Reaction times were generally 6 hr with pyridine, 24 hr with toluene, and several days with benzene. For the sole example reported with R<sub>1</sub> = trifluoromethyl (XV), several days refluxing in pyridine was required due to the deactivating influence of this group.

All of the compounds described in Table I gave satisfactory elemental analyses; purity was confirmed by tlc analysis while structures were verified by a combination of uv, ir, and nmr spectroscopy.

**Biological Results.** Results of antibacterial tests are shown in Table II, and it may be seen that only a few of the compounds have significant activity. The influence of the length of the side chain R is particularly important, with maximum overall activity found where R has 1-3 C atoms (I-III). Lengthening the chain has a drastic effect on the potency and V, with R having five C atoms, is completely inactive. Alterations of R involving the introduction of a branched chain (VII), unsaturated chain (IX), aryl (X), alkaryl (XI), or cycloalkyl (XIII) groups all resulted in a reduction of antibacterial properties. Substitutions in the oxazole ring, especially with phenyl groups,

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Table I. Compounds Synthesized

No.	R	R <sub>1</sub>	R <sub>2</sub>	Method	Yield, %	Mp, °C	Recrystn solvent	Empirical formula	Analyses <sup>a</sup>
I	-CH <sub>3</sub>	H	H	A	25	174-177	EtOH	C <sub>4</sub> H <sub>7</sub> N <sub>3</sub> OS	C, H, N
II	-CH <sub>2</sub> CH <sub>3</sub>	H	H	A	45	126-127	EtOH	C <sub>6</sub> H <sub>9</sub> N <sub>3</sub> OS	C, H, N, S
III	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	H	H	A	22	125-127	MeOH	C <sub>7</sub> H <sub>11</sub> N <sub>3</sub> OS	C, H, N, S
IV	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	H	H	A	27	120-121	EtOAc	C <sub>8</sub> H <sub>13</sub> N <sub>3</sub> OS	C, H, N, S
V	-(CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub>	H	H	A	12	77-78	CHCl <sub>3</sub>	C <sub>9</sub> H <sub>17</sub> N <sub>3</sub> OS	C, H, N
VI	-(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	H	H	A	13	96-97	CCl <sub>4</sub>	C <sub>10</sub> H <sub>19</sub> N <sub>3</sub> OS	C, H, N
VII	-CH(CH <sub>3</sub> ) <sub>2</sub>	H	H	A	16	118-120	MeOH	C <sub>7</sub> H <sub>11</sub> N <sub>3</sub> OS	C, H, N
VIII	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H	H	A	21	140-141	CHCl <sub>3</sub>	C <sub>8</sub> H <sub>13</sub> N <sub>3</sub> OS	C, H, N
IX	-CH <sub>2</sub> CH=CH <sub>2</sub>	H	H	C	24	82-85	EtOAc	C <sub>7</sub> H <sub>9</sub> N <sub>3</sub> OS	C, H, N

X	-C <sub>6</sub> H <sub>5</sub>	H	H	A	35	262-265	EtOH	C <sub>10</sub> H <sub>9</sub> N <sub>3</sub> OS	C, H, N
XI	-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	A	15	136-140	CHCl <sub>3</sub>	C <sub>11</sub> H <sub>11</sub> N <sub>3</sub> OS	C, H, N
XII	-CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	A	13	129-130	MeOH	C <sub>12</sub> H <sub>13</sub> N <sub>3</sub> OS	C, H, N, O, S
XIII	-C <sub>6</sub> H <sub>11</sub>	H	H	A	5	142-143	EtOAc	C <sub>10</sub> H <sub>13</sub> N <sub>3</sub> OS	C, H, N
XIV	-CH <sub>3</sub>	CH <sub>3</sub>	H	B	15	190-192	EtOAc	C <sub>6</sub> H <sub>9</sub> N <sub>3</sub> OS	C, H, N
XV	-CH <sub>2</sub> CH <sub>3</sub>	CF <sub>3</sub>	H	B	5	171-172	CCl <sub>4</sub>	C <sub>7</sub> H <sub>5</sub> F <sub>3</sub> N <sub>3</sub> OS	C, H, N
XVI	-CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	A, B	36, 40	229-230	CCl <sub>4</sub>	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> OS	C, H, N
XVII	-CH <sub>2</sub> CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	A, B	17, 20	196-198	CCl <sub>4</sub>	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> OS	C, H, N
XVIII	-CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	B	39	167-168	EtOH	C <sub>7</sub> H <sub>11</sub> N <sub>3</sub> OS	C, H, N, O, S
XIX	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	B	22	132-133	EtOH	C <sub>9</sub> H <sub>13</sub> N <sub>3</sub> OS	C, H, N, O, S
XX	-CH <sub>2</sub> CH=CH <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	C	7	149-150	CHCl <sub>3</sub>	C <sub>9</sub> H <sub>13</sub> N <sub>3</sub> OS	C, H, N, O, S
XXI	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	B	22	123-124	EtOH	C <sub>10</sub> H <sub>17</sub> N <sub>3</sub> OS	C, H, N

<sup>a</sup>All analyses are correct in each element noted to within  $\pm 0.3\%$ .

**Table II.** Antibacterial and Antifungal Activity *in Vitro*

No.	Minimum inhibition concentration, $\mu\text{g/ml}^{a,b}$																			
	A	B	C	D	E	F	G	H	J	K	L	M	N	O	P	Q	R	S	T	U
I	4	4	16	16	16	64	64	16	-	-	-	32	-	64	64	8	4	4	512	64
II	4	8	8	32	32	32	32	32	-	-	-	64	-	32	64	4	2	2	256	64
III	2	4	4	32	32	64	64	64	-	-	-	-	-	256	-	128	8	8	256	128
IV	4	4	8	512	-	-	-	-	-	-	-	-	-	64	-	32	32	32	512	128
V	-	-	-	-	-	-	-	-	-	-	-	-	-	64	-	16	8	512	256	32
VI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
VII	8	8	16	64	64	64	64	32	-	-	-	64	-	-	-	32	16	8	128	128
VIII	4	4	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IX	8	8	64	16	8	32	128	128	-	-	-	128	-	64	-	128	4	4	256	128
X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	128	128	-	-
XI	-	-	-	-	-	-	-	-	-	-	-	-	-	32	-	16	16	64	-	128
XII	-	-	-	-	-	-	-	-	-	-	-	-	-	64	-	16	16	64	-	128
XIII	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	32	64	32	-	64
XIV	16	16	32	-	512	-	-	-	-	-	-	-	-	256	32	32	4	8	128	16
XV	32	32	128	64	512	-	-	-	-	-	-	-	-	-	-	64	256	64	-	-
XVI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	256	-	-	-
XVII	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	128	-	-	-
XVIII	16	16	16	-	-	-	-	-	-	-	-	-	-	128	-	64	64	128	256	128
XIX	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	128	256	256	-	-
XX	256	256	-	-	-	-	-	-	-	-	-	-	-	512	-	128	128	128	-	-
XXI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cephalothin	0.25	0.25	16	0.5	16	8	8	0.25	2	512	-	1	-	8	256	0.25	0.125	0.125	0.06	64
Benlate	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

<sup>a</sup>(-) indicates  $>512 \mu\text{g/ml}$ . <sup>b</sup>Bacterial cultures: A, *Staphylococcus aureus*; B, *Staphylococcus aureus*; C, *Streptococcus faecalis*; D, *Aerobacter aerogenes*; E, *Brucella bronchiseptica*; F, *Escherichia coli*; G, *Escherichia coli*; H, *Klebsiella pneumoniae*; J, *Proteus morganii*; K, *Proteus vulgaris*; L, *Pseudomonas aeruginosa*; M, *Salmonella typhimurium*. Fungal cultures: N, *Candida krusei*; O, *Cryptococcus neoformans*; P, *Saccharomyces cerevisiae*; Q, *Trichophyton mentagrophytes*; R, *Botrytis cinerea*; S, *Colletotrichum atramentarium*; T, *Penicillium expansum*; U, *Alternaria tenuis*.

**Table III.** Activities in Plant Disease Tests

Compd no.	Test type <sup>b</sup>	Activity ratings <sup>a</sup> against plant diseases (foliage application)				Test type <sup>b</sup>	Activity ratings <sup>a</sup> against plant diseases (soil application)			
		LB <sup>c</sup>	RB <sup>c</sup>	A <sup>c</sup>	H <sup>c</sup>		RN <sup>c</sup>	FRR <sup>c</sup>	DOP <sup>c</sup>	VW <sup>c</sup>
I	D-1	4	5		4					
	D-2	2	3		2					
	D-3	1	1		2					
II	D-1	5	5	5	3	E-1	2	1	1	
	III	D-1	1	5	4	4	E-1	5	5	5
E-2								2	4	
E-3									4	
IV	D-1	1	5	4	4	E-1	4	2	3	
	V	D-1	3	4	4	4	E-1	1	3	3
VI	D-1	2	4	4	3					
	VII	D-1	1	3	5	1	E-1	4	3	4
E-2							1		3	
VIII	D-1	2	4	5	4					
	IX	D-1	1	5	4	3	E-1	1	5	3
E-2								4		
XI	D-1	1	5	4	3	E-1	1	4	4	
						E-2			4	
						E-3			1	
XII	D-1	2	5	4	4	E-1	1	1	1	
	D-2		2	1	1					
XIII	D-1	1	1	1	1	E-1	1	2	1	
	XIV	D-1	5	4	4	3	E-1	1	4	5
E-2								1	5	
E-3									5	
XVI	D-1	1	1	1	1	E-1	4	1	1	
XVII	D-1	1	3	1	1	E-1	5	1	1	
						E-2	1	1	1	
						E-1	1	1	4	
XVIII	D-1	3	3	4	1					
	D-2		2	2						
XIX	D-1	1	4	3	3	E-1	4	1	5	
	D-2		2	1	1	E-2			4	
XXI	D-1	3	3	4	3					
Maneb	D-1	4	4	5	4					
Cynem						E-1	5			
Lanstan						E-1		4	5	
Benlate						E-1			5	

<sup>a</sup>Disease severity rating: 1 = severe, 2 = moderately severe, 3 = moderate, 4 = slight, 5 = none. <sup>b</sup>Test types: D-1 = 400 ppm, D-2 = 80 ppm, D-3 = 16 ppm, E-1 = 40 lb/acre, E-2 = 20 lb/acre, E-3 = 10 lb/acre. <sup>c</sup>Plant diseases: LB = tomato late blight (*Phytophthora infestans*), RB = rice blast (*Piricularia oryzae*), A = cucumber anthracnose (*Colletotrichum lagenarium*), H = helminthosporium leaf spot on barley (*Helminthosporium sativum*), RN = root knot nematode (cucumber), FRR = fusarium root rot (bean), DOP = pythium damping off (cotton), VW = verticillium wilt (cotton).

had a similar result. The active compounds had a lower degree of activity toward gram-negative organisms than gram-positive organisms.

Results of antifungal testing, also shown in Table II, indicate activity of a much greater extent, with most of the compounds having some effect. The pattern of activity is, however, more complex with structure-activity relationships more difficult to discern. Compound II was the best overall fungicide, and all alterations in structure resulted in reduced potency. Lengthening the side chain R had a variable effect, giving compounds which were more efficient against some fungi but less efficient against others. The same variable effects were found by the introduction of branched or unsaturated side chains. In general, substitutions in the oxazole ring reduced activity. The thioureas displayed greatest effect against the R organism (*Botrytis cinerea*).

In greenhouse trials (Table III) the thioureas showed an interesting spectrum of activity against the common plant foliage and soil pathogens listed. The structure-activity pattern appeared similar to that for the *in vitro* antifungal results. However, although compound II has the best overall activity against plant foliage pathogens, compound III is clearly the best against plant soil diseases. The uniform activity of the latter against the four pathogens chosen, in contrast to the limited activities of the reference fungicides cynem, lanstan, and benlate, is worthy of note.

## Experimental Section

**Typical Preparations of Compounds in Table I. Method A.** 1-Ethyl-3-(2-oxazolyl)thiourea (II). Ethyl isothiocyanate (4.78

g, 0.055 mol) was added to a solution of 2-aminooxazole (4.2 g, 0.05 mol) in dry pyridine (25 ml), under nitrogen, and the mixture was heated under reflux for 6 hr. Removal of the solvent gave a dark oil which, following solution in ethanol and treatment with charcoal, yielded a crystalline product, further purified by crystallization from ethanol: yield 3.7 g (44%); mp 126-127°.

**Method B.** 1-Methyl-3-(4,5-dimethyl-2-oxazolyl)thiourea (XVIII). Methyl isothiocyanate (8.0 g, 0.11 mol) was added to a solution of 2-amino-4,5-dimethyloxazole (11.2 g, 0.1 mol) in dry toluene (150 ml). The mixture was heated under reflux for 24 hr, and the solvent was then removed to give a yellow solid, which was recrystallized from ethanol (charcoal treatment): yield 7.2 g (39%); mp 167-168°.

**Method C.** 1-Allyl-3-(2-oxazolyl)thiourea (IX). Allyl isothiocyanate (10.9 g, 0.11 mol) was added to a solution of 2-aminooxazole (8.4 g, 0.1 mol) in dry benzene (200 ml) and the mixture was heated under reflux for 4 days. Removal of solvent gave a solid mass purified by recrystallization (twice) from ethyl acetate (charcoal treatment): yield 4.4 g (24%); mp 82-85°.

**Methods Used in Biological Tests.** (a) General. The gradient-plate method was used in which each compound was distributed in the appropriate agar medium to form a wedge. Agar without compound was poured on top of this wedge to give a flat surface in which the compound, after diffusion, was distributed at a decreasing concentration. Top concentration was 512 µg/ml and it was found that each plate could be effectively read down to 1/8 of top concentration. Plates were therefore also prepared with top concentration of 64 and 8 µg/ml. This covered the concentration range from 512 to 1 µg/ml which was sufficient for the testing of these compounds.

When the surface of the agar was dry, the plates were inoculated with a swab soaked in the appropriate culture. After incubation, the minimum inhibitory concentration was read as the lowest concentration of the compound at which there was no growth of the particular culture. These readings were taken to the nearest doubling dilution of the compound.

(b) **Antibacterial.** Nutrient broth was used to grow the cultures and nutrient agar for the plates. Incubation was at 37° overnight.

(c) **Antifungal.** Sabouraud agar was used for the cultures and the plates. Sabouraud broth was used to wash off the culture for inoculation. Incubation was at 27° for 3–4 days.

(d) **Plant Disease. Foliage Tests.** Test plants were sprayed with aqueous emulsions of the compounds followed by inoculation with cultures of plant pathogens. The test plants were grown in a greenhouse under standard conditions of temperature and humidity, and after a suitable period the severity of the plant diseases was measured with reference to controls.

(e) **Plant Disease. Soil Results.** Compounds were incorporated into soil at the levels indicated. Test plants treated with plant pathogenic cultures were grown under standard conditions in a greenhouse, and after a suitable period disease conditions were measured with reference to controls.

## References

- (1) G. Crank and M. J. Foulis, *J. Med. Chem.*, **14**, 1075 (1971).
- (2) G. W. Anderson, U. S. Patent 2,362,337 (1944); *Chem. Abstr.*, **39**, 2516 (1945).
- (3) R. Gompfer and O. Christman, *Chem. Ber.*, **92**, 1944 (1959).

## 5-Hydroxymethyltubercidin. Synthesis, Biological Activity, and Role in Pyrrolopyrimidine Biosynthesis†

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Three naturally occurring 4-amino-7-( $\beta$ -D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine nucleosides have been isolated from the *Streptomyces* (for review see ref 2). They are tubercidin, toyocamycin, and sangivamycin. These three nucleoside antibiotics are structural analogs of adenosine in which N-7 of the imidazole ring has been replaced by a carbon atom. These antibiotics have significant antibacterial, antiviral, and anticancer activity in experimental animal systems.<sup>2-11</sup> The chemical reactivity of a number of pyrrolopyrimidine ribonucleoside analogs has also been studied.<sup>2,12-15</sup> Studies on the biosynthesis of these pyrrolopyrimidine nucleosides show that the carbon-8 of GTP is lost as formic acid; carbons 1', 2', and 3' of the ribosyl moiety serve as the carbons of the pyrrole ring and the cyano group of toyocamycin.<sup>2,16</sup> These biological and biosynthetic properties of the pyrrolopyrimidine nucleosides prompted the present study to determine the effect of a hydroxymethyl group on C-5 of tubercidin and to determine if 5-hydroxymethyltubercidin is involved in the biosynthesis of toyocamycin and if there is a difference in the toxicity of toyocamycin and 5-hydroxymethyltubercidin against bacterial and mammalian cells. The results describe (1) the synthesis of 5-hydroxymethyltubercidin by two methods, (2) the biological properties of 5-hydroxymethyltubercidin in leukemia L-1210 cells and bacterial cells, and (3) studies on the biosynthesis of toyocamycin (Scheme I).

## Experimental Section‡

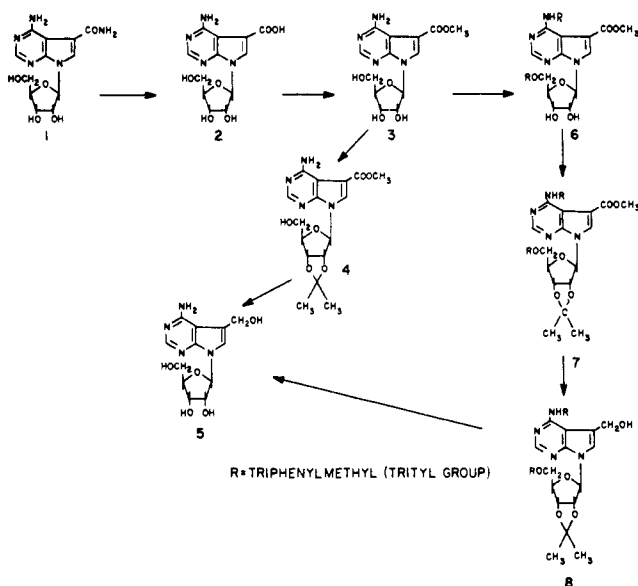
**Method 1.** Tubercidin-5-carboxylic acid (2) and methyl tuber-

†Paper 15. For the previous paper in this series, see ref 1.

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‡Infrared, ultraviolet, and mass spectra were recorded with a Perkin-Elmer 437 gradient spectrophotometer and a Beckman Model DB spectrophotometer. Samples were introduced by direct inlet probe at 274°. Melting points were taken with a Thomas-Hoover silicone bath apparatus and are uncorrected. Elemental analyses were performed by Huffman Laboratory, Wheatridge, Colo.

## Scheme I. Synthesis of 5-Hydroxymethyltubercidin (5) by Methods 1 and 2



cidin-5-carboxylate (3) were prepared from sangivamycin<sup>§</sup> by the method of Rao.<sup>16</sup>

**Methyl 2',3'-O-Isopropylidene-5-carboxylate (4).** Compound 3 (371 mg, 1.14 mmol) was added to a solution of *p*-toluenesulfonic acid monohydrate (400 mg, 2.29 mmol) and 2,2-dimethoxypropane (1.5 ml) in 14 ml of acetone. The reaction mixture was passed through an AG 1-X8 acetate column (10 ml, 1 cm diameter). Elution of 4 was done with 150 ml of methyl alcohol. The effluent was concentrated to syrup *in vacuo* (45°). The syrup was dissolved in chloroform (10 ml) and added to a silicic acid column (50 ml, 8 × 2.5 cm, in chloroform). The column was washed with 300 ml of chloroform. Compound 4 was eluted with 135 ml of ethyl acetate-chloroform (25:75, v/v). The eluent was concentrated to a syrup (under vacuum, 40°). Compound 4 was crystallized from ethyl ether and recrystallized from ethanol-water (30:70, v/v): yield, 381 mg (1.046 mmol); 91.5%; mp 194.5–195.5°; uv  $\lambda_{\max}$  (chloroform) 282 nm ( $\epsilon$  17,600). 4 was analyzed correctly for C<sub>16</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub>. Unreacted compound 3 was eluted from the column with 200 ml of methanol-chloroform (50:50, v/v): yield, 14 mg (0.05 mmol).

**5-Hydroxymethyltubercidin (5).** Compound 4 (58 mg, 0.16 mmol) was suspended in 5 ml of ethyl ether (distilled over lithium aluminum hydride). The suspension was stirred and three 20-mg portions of lithium aluminum hydride were added at 2, 4, and 6 hr. The mixture was stirred an additional 12 hr. The excess lithium aluminum hydride was filtered through silica gel on a millipore filter. The insoluble residue was washed with 100 ml of acetone-water (50:50, v/v). The combined filtrates and washings were concentrated to dryness. The residue was taken up in 10 ml of acetic acid-water (80:20, v/v) and refluxed for 2.5 hr. The mixture was evaporated to dryness and dissolved in 5 ml of water. The solution was added to an AG hydroxide column (5 ml, 1 cm diameter). The column was washed with 100 ml of methanol-water (70:30, v/v) in tubes 17–28 (10-ml fractions). The tubes were combined and evaporated to dryness under vacuum (40°). 5 was crystallized from water: yield, 23 mg; 48%; mp 229–230°; uv  $\lambda_{\max}$  (water) 272 nm. There was no melting point depression of a mixture of 5 synthesized by method 2. The mass spectra of 5 showed a parent ion at 296.

**Method 2. Methyl N<sup>4</sup>,5'-O-Ditryltubercidin-5-carboxylate (6).** Compound 3 (440 mg, 1.36 mmol) was added to 7 ml of dry pyridine. Triphenylmethyl chloride (630 mg, 2.10 mmol) was added with stirring at room temperature; an additional 510 mg (17 mmol) of triphenylmethyl chloride was added at 50 hr and the reaction continued for an additional 39 hr. Methyl alcohol (5 ml) was added; the mixture was allowed to stand for 3 hr and evaporated *in vacuo* to a colorless syrup. Chloroform (50 ml) was added and mixed with 2 g of silicic acid and dried *in vacuo* (under 40°). This mixture was added to a column of silicic acid (100 ml, 2.5 × 10 cm). The column was washed with 200 ml of lig-

<sup>§</sup>Sangivamycin was isolated from *Streptomyces rimosus*; see ref 17.