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SYNTHESIS OF PURINE NUCLEOSIDE
AND
NUCLEOTIDE ANALOGS AS ANTIPARASITIC AGENTS

ANNUAL REPORT 1 AND FINAL REPORT

John P. Neenan, Ph.D.
1 September 1979

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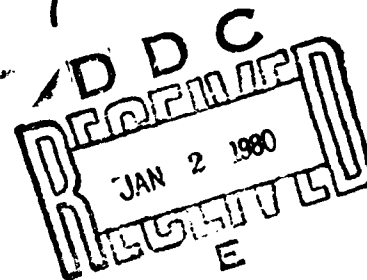
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SUMMARY

The purpose of the research was to conduct studies on the synthesis of purine nucleoside and nucleotide analogs as anti-parasitic agents. The primary target compounds were 5'-deoxytubercidin 5'-amino-5'-deoxytubercidin (nucleoside analogs) and 5'-fluoro-5'-deoxytubercidin (a nucleotide analog.)

One target, 5'-deoxytubercidin, was successfully prepared in an efficient two-step procedure and submitted for screening.

Several attempts to prepare the 5'-amino- and 5'-fluoro-derivatives of tubercidin either by direct routes or via blocked tubercidin were unsuccessful. Due to problems encountered in these attempted syntheses, work on 5'-derivatives of two other purine nucleoside antibiotics - puromycin aminonucleoside and 6-methylmercaptapurine riboside - was not initiated. However, work on 5'-derivatives of nebularine was performed and some success was achieved in this series.

Nebularine was synthesized by a literature method and submitted for screening. A two-step synthesis of 5'-deoxynebularine from nebularine via 5'-deoxy-5'-iodonebularine was accomplished even though an analytical sample is not yet in hand.

Additional 5'-deoxytubercidin and its synthetic precursor, 5'-chloro-5'-deoxytubercidin were prepared when attempts to synthesize the 5'-amino- and 5'-fluoro- derivatives had to be abandoned because the contract was close to termination. Unfortunately, these samples are not analytically pure as of this report.

In summation, 1.6g of nebularine and over 600 mg of 5'-deoxytubercidin were submitted for screening during the project. Additional 5'-deoxytubercidin as well as samples of 5'-chloro-5'-deoxytubercidin and 5'-deoxynebularine are in hand but require further purification.

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FOREWORD

This research was conducted under contract No. DAMD17-78-C-8058 during the period 1 September 1978 to 31 August 1979. Dr. John P. Neenan served as Principal Investigator. Four undergraduate students conducted the research under Dr. Neenan's supervision: Stephen Andracki, Steve Howard, Peter Lodestro, and Walter Vogt. Stephen Andracki and Steve Howard worked on the project through its entire period, and the accomplishments of the project are largely attributable to their superlative effort. Peter Lodestro served as replacement for Walter Vogt, who had to leave the project because of a heavy course load. Peter filled an important logistic niche as supplier of nebularine via catalytic reduction of 6-chloropurine riboside.

Grateful acknowledgements are also due to Drs. Pete Johnson at Illinois Institute of Technology, Malcolm MacCross at Argonne National Laboratory and Henry Winkler at Illinois Benedictine College for their assistance with NMR spectra of the target compounds.

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TECHNICAL PRESENTATION

BACKGROUND

A number of purine nucleoside antibiotics such as puromycin aminonucleoside and tubercidin are known antiparasitic agents.¹⁻⁴ Jaffe has proposed that the susceptibility of pathogenic helminths and protozoa to fraudulent purine, in contrast to pyrimidine, nucleosides probably results from a deficiency in enzymes that synthesize the purine ring *de novo*. Unfortunately these antibiotics can become incorporated into mammalian nucleic acids and hence are toxic to host cells.

The purpose of this research effort was to modify the parent nucleosides such as tubercidin at 5'-carbon by removal of the hydroxyl group, which is phosphorylated by kinases to provide nucleoside 5'-triphosphates for DNA and RNA synthesis. The hydroxyl group would be replaced by hydrogen, by amino to afford nucleoside analogs,^{5,6} or fluorine to yield nucleotide analogs. The resultant 5'-substituted derivatives are thus designed to inhibit nucleoside and nucleotide kinases as well as other parasitic enzymes.

Mammalian cells, on the other hand, could conceivably override such metabolic blockades, especially those imposed on salvage nucleoside kinases, because host cells can synthesize purine nucleotides *de novo* and are not restricted to salvage synthesis pathways. Here then is a means for achievement of selective toxicity against parasites.

CHEMISTRY

Borchardt et al.⁸ first converted tubercidin (compound 1, scheme 1) to 5'-chloro-5'-deoxytubercidin (2) in 37% yield by use of the direct halogenation method of Kikugawa and Ichino.⁹ By use of this method and by cold temperature isolation procedure, we prepared compound 2 quantitatively. (See the Experimental Section.)

Dechlorination of 2 by the method of Wang and Hogenkamp then afforded target 5'-deoxytubercidin¹⁰ (3). The overall yield of crystalline and chromatographically homogeneous 3 was repeatedly found to be 49%. However, recrystallization was always required to afford analytically pure material.

In our last scaled-up preparation of 3, over 1.5g of 5'-deoxytubercidin was obtained - again in 48% overall yield. Unfortunately a large amount of product was lost when the flask broke during recrystallization. Over half the product was recovered, chromatographed over Dowex [H⁺] ion-exchange resin, and crystallized from reagent alcohol. However, the final analysis of this sample showed that it still required recrystallization. (Calcd. for C₁₁H₁₄N₄O₃: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.37; H, 5.67; N, 19.29).

Two analytically pure samples of 5'-deoxytubercidin were previously submitted for screening.

Both 5'-deoxytubercidin and the chloro intermediate 2 were characterized by NMR. Their spectra resembled those of other 5'-deoxynucleosides and 5'-chloro-5'-deoxynucleosides reported by Wang and Hogenkamp.¹⁰ The IR spectra were largely

uninformative except in the case of compound 2 where a C-Cl stretching band at 610cm^{-1} was observed. This peak was absent in the ir spectrum of 5'-deoxytubercidin (3), which also gave a negative Beilstein flame test in contrast to chloro-derivative 2. The UV spectra of both 2 and 3 were indistinguishable from that of tubercidin.

To ensure the isomeric purities of compounds 2 and 3, small samples of each were converted quantitatively to the corresponding 2,'3'-O-isopropylidene derivative, (4 and 5) which ran with the solvent front on thin-layer chromatograms (Table I). Any 2'-or 3'-substituted tubercidin in the samples would not have formed an isopropylidene derivative.

Compound 2 decomposes in boiling water to form at least two products as observed on tlc. The half-life of 2 under those conditions is less than 2 hours. Presumably, the pathway of decomposition is initial formation of the N³,5'-cyclonucleoside-5'-cyclonucleoside^{11,12} followed by ring opening of the aglycone. Even at room temperature, 3 gradually decomposes so it is best stored in a freezer. Compound 2 on the other hand is quite stable to prolonged boiling water, and thus can be sterilized and conveniently stored at room temperature.

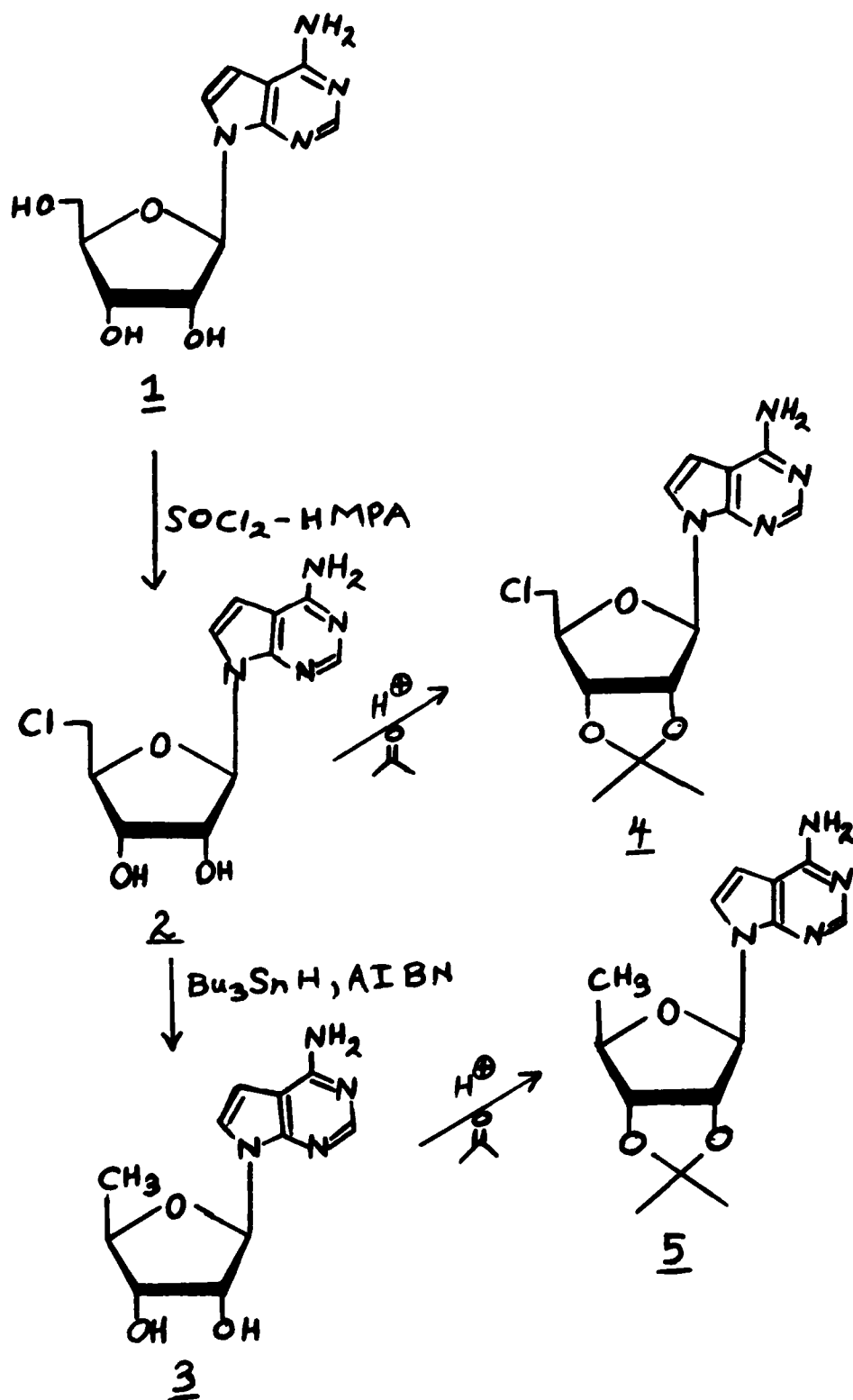
Compound 3 was first prepared in low yield by Anzai and Matsui¹² via a grueling six-step route from tubercidin. These workers had to resort to column chromatography repeatedly for isolation of intermediates from product mixtures. In contrast, the route we report can afford 5'-deoxytubercidin in good yield requires only one ion-exchange chromatography, and is easily reproducible.

Our various unsuccessful attempts to prepare 5'-deoxy-5'-fluorotubercidin and 5'-amino-5'-deoxytubercidin were largely discussed in the quarterly reports. We will summarize these efforts briefly and cover work done since the last report.

Encouraged by the successful synthesis of 5'-chloro-5'-deoxytubercidin with SOCl_2 -hexamethylphosphoramide (HMPA) reagent,^{8,9} we made several attempts to prepare 5'-deoxy-5'-fluorotubercidin analog with SOF_2 -HMPA either in a bomb or in a three-neck flask. At first we were encouraged because even though much decomposition occurred, one product has an R_x value identical to compound 2 in several tlc and paper chromatography systems. We expected that the desired 5'-fluoro-derivative would indeed have an R_x similar to 2. After extensive paper chromatography we isolated this product and found it to be identical to 2 not only by chromatography, but by NMR, by its half-life in boiling H₂O, and finally by elemental analysis. Both the SOF_2 we prepared ourselves and that which we purchased contained SOCl_2 used in synthesis.¹³

Other attempts to prepare the fluoro derivative employed diethyl (2-chloro-1,1,2-trifluoroethyl) amine (CTT)-- a reagent for direct conversion of hydroxyl to fluoro in steroids and cephalosporine.¹⁴ In repeated experiments, we treated tubercidin with freshly prepared CTT in either DMF or HMPA. No product having the expected mobility on tlc of the desired product was found. Indeed both tubercidin and nebularine were largely inert to this reagent.

SCHEME I



Several unsuccessful attempts during the summer were made to prepare 5'-O-p-nitrobenzenesulfonyl tubercidin by the method of Hampton¹⁵ in hopes that subsequent reaction in situ with tetrabutylammonium fluoride or azide into the 5'-carbon-the resultant 5'-azido-5'-deoxytubercidin would have served as synthetic precursor to target 5'-amino-5'-deoxytubercidin. In one experiment with lithium azide we subjected the crude reaction mixture to catalytic hydrogenation and tlc showed that a trace ninhydrin-positive spot had formed which may have been the desired 5'-amino-5'-deoxytubercidin. We could not reproduce this result.

Attempts to prepare either 5'-azido-5'-deoxytubercidin or the corresponding nebularine derivative by a recently reported one-step method¹⁶ also failed.

Attempts to selectively block the 6-amino group with benzoyl or acetyl by the method used on cytidine by Watanabe and Fox¹⁷ lead to incomplete reaction. Thus, when tubercidin was refluxed in methanol in the presence of acetic anhydride most of the tubercidin remained unreacted as monitored by tlc.

The pK of the 6-amino group in tubercidin is higher than that of the 4-amino in cytidine, and presumably protonation inhibits the reaction. Attempts to drive the reaction forward by addition of pyridine as proton scavenger and excess acetic anhydride led to peracetylation as judged by tlc.

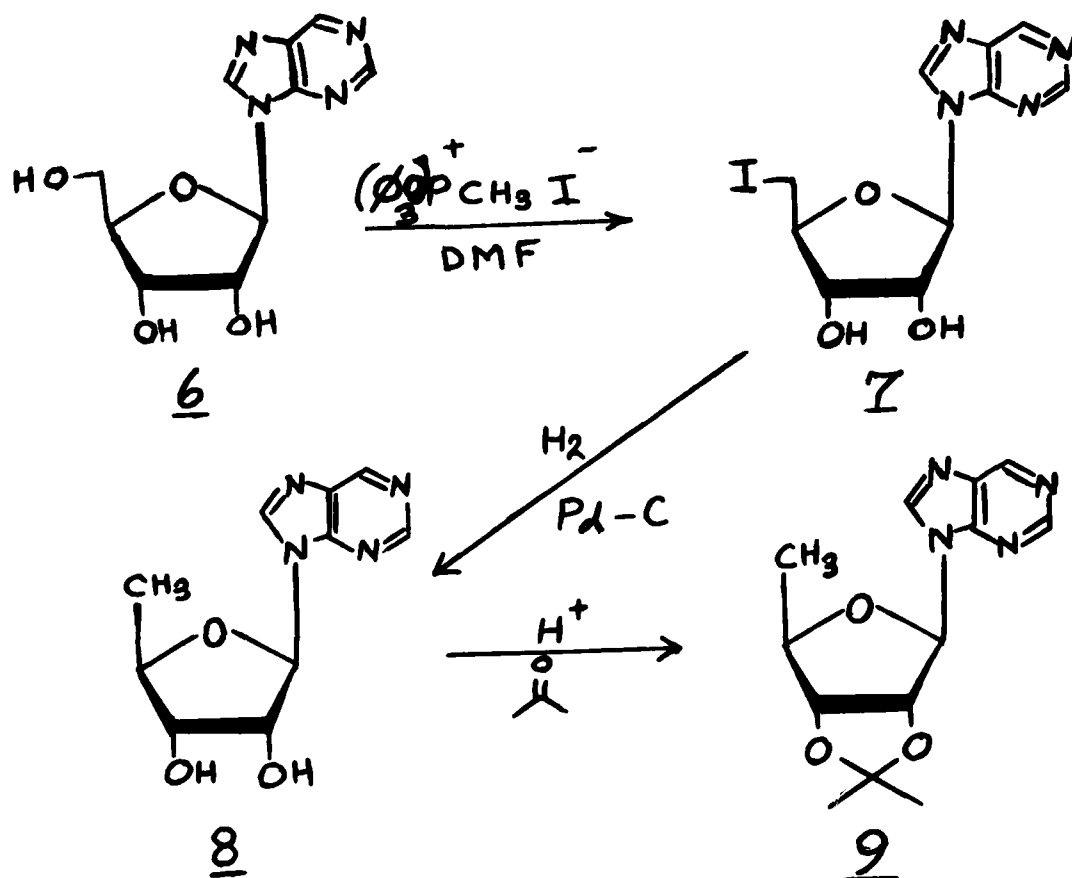
Faced with a severe time constraint we decided to abandon work in the tubercidin series and turn our attention to the nebularine series where we encountered some success.

Treatment of nebularine (6)¹⁸ with methyltriphenoxy-phosphonium iodide²⁰ in DMF led to complete reaction and formation of a major product which was isolated by extraction, paper chromatography, and finally column chromatography. Due to the extensive work-up procedure and reluctance on the part of the product to crystallize, the yield was low. Nevertheless, we have evidence that the product isolated was indeed 5'-iodo-5'-deoxynebularine (compound I, Scheme II).

The product has the same UV spectrum in acid, base, and water as nebularine itself.¹⁸ As expected of a less polar compound it is homogeneous and moves faster on tlc than nebularine. NMR did not confirm the structure but, on the other hand, was not incompatible with it. An analytically pure sample was not obtained even though attempts were made to crystallize the product from several solvents - even after repeated chromatography. Elemental analysis did, however, confirm the presence of iodine, which was also found by the silver nitrate test.

We decided to convert 7 to 5'-deoxynebularine (8) by catalytic hydrogenation over Pd on carbon in the presence of sodium acetate. The reaction was quantitative. Thus, a single new derivative (8) of nebularine of lower R_f than 7 was observed on tlc. The product was chromatographed over a silica gel column and attempts were made to crystallize but only sodium acetate was obtained in this manner. The mother liquors were condensed to a brown residue which according to UV contains over 600 mg of target compound 8, the structure of which was assigned by UV, tlc, and quantitative isopropylidenation to 9. Thus, while we do not have a crystalline sample of 5'-deoxynebularine as of this final report, the route to it is apparently feasible. (Scheme II).

SCHEME II



RECOMMENDATIONS

The Principal Investigator will submit a new contract proposal from the University of Arizona with revised routes to 5'-amino-5'-deoxytubercidin and 5'-fluoro-5'-deoxytubercidin. He is also willing to try to obtain analytically pure samples of 5'-deoxynebularine, 5'-chloro-5'-deoxytubercidin, and additional 5'-deoxytubercidin for screening from material now in hand. Probably these samples only require recrystallization.

EXPERIMENTAL SECTION

Melting points were obtained on a Mel-Temp block and are uncorrected. In most cases melting points were variable and prior softening was encountered even with analytically pure samples. Therefore, UV and tlc were used as prime criteria of purity. Tlc was performed on Eastman 13254 cellulose with fluorescent indicator in Systems: A (1-butanol-H₂O, 7:2:1, v/v), and C (1-butanol-EtOH-H₂O, 10:3:7:, v/v). R_F values of the compounds are contained in Table I. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. 6-chloropurine riboside was purchased from Sigma. Tubercidin was purchased mainly from Sigma but, when this supplier was out of stock, from Vega Biochemicals or P-L Biochemicals.

5'-chloro-5'-deoxytubercidin⁸ (2). - The general method of Kikugawa and Ichino⁹ was followed with modification only in the isolation procedure. To a stirred, chilled solution of dry 1 (5.0g, 18.8 mmole) in 50 ml of dry hexamethylphosphoramide was added 7.5 ml of freshly distilled SOCl₂. After 18 hours at 70° the red mixture was poured into 450 ml of ice-cold H₂O. The suspension was chromatographed over Dowex 50w-x4 [H+] resin by elution with H₂O until the eluate was no longer acidic, and then with a linear gradient of 0.1-2N NH₄OH. The fractions which had max at 270nm were pooled. Evaporation of solvent in vacuo below 35° followed by drying under high vacuum at room temperature gave 5.34g (100%) of amorphous white powder, homogeneous on tlc in systems A, B, and C. $\lambda_{\text{max}}^{0.1N \text{ NH}_4\text{OH}}$ 270 nm, $\epsilon=610 \text{ cm}^{-1}$ (C-Cl stretch). mp 140-42° (prior softening). NMR(DMSO-D₆) δ 3.9 (m, 2H, C₅'-H), 4.1 (m, 2H, C₂'-H and C₃'-H), 4.5 (m, 1H, C₄'-H), 5.4 (br, 2H, OH), 6.0 (d, 1H, C₁'-H), 6.9 (br, 2H, -NH₂), 6.6, 7.3 (2s, 2H, C₇-H and C₈-H), 7.9 (s, 1H, C₂-H).

A sample of 2 isolated during attempted synthesis of 5'-deoxy-5'-fluoro-tubercidin (see text) gave the following elemental analysis for C₁₁H₁₃ClN₄O₃ (MW=284.70).

	PERCENT			
	C	H	N	Cl
Theory:	46.41	4.60	19.68	12.45
Found:	46.43	4.46	19.40	13.12

5'-Deoxytubercidin¹² (3)- Compound 3 was prepared by the general method of Wang and Hogenkamp.¹⁰

To a stirred solution of dry 2 (1.0g, 3.5mmole) in THF (freshly distilled from sodium and dried over molecular sieves) was added 4g (13.8 mmole) of tributyltin hydride (Alpha Inorganics) and 0.25g (1.5 mmole) of azobis (isobutyronitrile) (AIBN, Aldrich). The mixture was refluxed under N₂ for 24 hr. The solvent was removed in vacuo and the residue solidified by addition of cold petroleum ether. The crude product was collected by filtration, washed with 100 ml cold petroleum ether, and recrystallized twice from reagent alcohol to give 0.31g (30%) of white crystals, mp 182-84° (prior softening) $\lambda_{\text{max}}^{0.1N\text{NaOH}}$ = 270 nm (ϵ_{max} - 1.2x10⁴). Homogeneous in the systems A,B, and C. IR and NMR spectra were compatible with the structure*. Anal. For C₁₁H₁₄N₄O₃ (MW=250.26):

	% C	% H	% N
Calcd:	52.79	5.64	22.39
Found:	52.39	5.68	22.09

5'-Deoxy-2',3'-O-isopropylidenetubercidin (5). - The general procedure of Wechter and Hanze¹⁹ was employed.

To a stirred solution of 10mg of 3 in 1.0ml of dry acetone and 0.2ml of 2,2-dimethoxypropane was added 30 mg of p-toluenesulfonic acid. After 2 hrs. tlc showed complete disappearance of 3 and formation of a new product (5) which was homogeneous and moved with the solvent front (Table 1).

5'-Deoxy-5'-iodonebularine (7). - A solution of 14.9g (33 mmoles) of methyltriphenoxyposphonium iodide²⁰ in DMF (83ml, total volume) was added via an additional funnel to a 200ml chilled flask containing 5.6g (22 mmoles) of dry nebularine.¹⁸ The reaction mixture was stirred for 6 hrs in an ice-bath. More Rydon reagent²⁰ (4.5g in 25ml of DMF) was then added. After 3 hrs, the mixture was poured into 300 ml of 10% aqueous sodium thiosulfate, extracted with ethyl acetate (9x200ml). Organic layers were pooled and concd in vacuo to give a yellow oil, which was dissolved in 25ml of DMF and chromatographed on 32 sheets of Whatman 3MM paper in System C. The fastest band was phenol. Strips containing the product band, which moved between phenol and unreacted nebularine, were eluted by descending chromatography in 2-propanol-H₂O (7:3, v/v). The eluate was collected in beakers, pooled, and concd in vacuo to give a yellow oil, which was dissolved in 100ml of CHCl₃-MeOH (3:1, v/v) and applied to a column of 300g of silica gel prepared with CH₂Cl₂-MeOH (15:1, v/v) and eluted with the same solvent system. Fractions 3-16 (100 ml ea) were found by uv to contain product, were pooled and evaporated to give 0.96g of a tan powder which could not be recrystallized from any of several solvents but was chromatographically homogeneous and had the same uv spectrum as nebularine ($\lambda_{\text{max}}^{0.01N\text{NaOH}}$ =262nm). A small sample of 7 was found by tlc to decompose completely after 6 hr in boiling H₂O to give nebularine and a product presumed to be N³,5'-cyclonebularine (Rf=0.41 in system A). In this property compound 7 thus resembles other 5'-deoxy-5'-iodonucleosides^{12,20}. Compound 7 was used without further purification for the next step.

*The NMR spectrum resembled that of other 5'-deoxynucleosides. See ref. 10.

5'-Deoxynebularine 8. - To a stirred solution of 1.2g (3.4 mmoles) of crude 7 in 40ml of ethanol was added 600mg of 5% Pd on charcoal and 3.0g of sodium acetate. Hydrogenation was conducted overnight at ambient temperature and pressure. When tlc showed the reaction was complete, the catalyst was removed by filtration and washed thoroughly with hot ethanol. The filtrate was evaporated to dryness to give a yellow solid which was taken up in 50ml of CHCl₃-MeOH (1:1 v/v) and applied to a column of 200g of silica gel, prepared in and eluted with CH₂Cl₂-EtOH (15:1, v/v). Twenty-eight fractions (200ml each) were collected. Fractions 16-26 were found by uv to contain the product and were pooled and evaporated to give a white-gray solid. Attempted recrystallization from 1-propanol gave only sodium acetate. Mother liquors containing 8 were evaporated to give a brown residue, which awaits further purification. A small sample of 8 was quantitatively converted to isopropylidene derivative 9 as confirmation of structure. (Table I). Table II contains a list of samples submitted to Walter Reed Army Institute of Research during the course of the project.

TABLE I

Rf Values of Tubercidin and Nebularine Derivatives

<u>Compound No.</u>	<u>SYSTEM</u>		
	<u>A</u>	<u>B</u>	<u>C</u>
<u>1</u>	0.49	0.73	0.67
<u>2</u>	0.77	0.84	0.78
<u>3</u>	0.72	0.81	0.74
<u>4</u>	0.99	0.99	0.99
<u>5</u>	0.99	0.99	0.99
<u>6</u>	0.50	0.75	0.67
<u>7</u>	0.88	0.90	0.87
<u>8</u>	0.85	0.92	0.81
<u>9</u>	0.99	0.99	0.99

TABLE II

Compounds Submitted for Antiparasite Screening During Contract Period**

<u>Compound</u>	<u>Sample No.</u>	<u>WR Bottle No.</u>	<u>Amount</u>
Nebularine	PL-I-12	BJo8205	1.6g
5'-Deoxytubercidin	SA-32	BJ30583	343mg
5'-Deoxytubercidin	SA-41	BJ30592	257mg

**Submitter key no. 1269. Samples of 5'-deoxynebularine, 5'-chloro-5'-deoxytubercidin, and additional 5'-deoxytubercidin will be submitted if the principal investigator can render them analytically pure by recrystallization of material now in hand.

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) In this research studies on the synthesis of purine nucleoside and nucleotide analogs as antiparasitic agents were conducted. Primary target compounds were 5'-deoxytubercidin 5'-amino-5'-deoxytubercidin and 5'-fluoro-5'-deoxytubercidin. One target, 5'-deoxytubercidin was successfully prepared in an efficient two-step procedure and submitted for screening. Attempts to prepare the 5'-amino- and 5'-fluoro-derivatives of tubercidin by direct routes or via blocked tubercidin were unsuccessful. Work on 5'-derivatives of nebularine was performed and some success was achieved in this series. A two-step synthesis of 5'-deoxynebularine from nebularine via		

Block 20 - (continued)

5'-deoxy-5'-iodonebularine was accomplished.

Additional 5'-deoxytubercidin and its synthetic precursor, 5'-chloro-5'-deoxytubercidin were prepared. These samples are not analytically pure as of this report.

In summation, 1.6g of nebularine and over 600 mg of 5'-deoxytubercidin were submitted for screening during the project. Additional 5'-deoxytubercidin as well as samples of 5'-chloro-5'-deoxytubercidin and 5'-deoxynebularine are in hand but require further purification.

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