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NAPHTHYRIDINE ANTIMALARIAL AGENTS

ANNUAL TECHNICAL REPORT

for

April 1, 1974 - March 31, 1975

by

JOHN F. PILOT

(201 - 474-3962)

APRIL, 1975

Sponsored By

UNITED STATES ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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60 sixty-one compounds comprising a variety of target structures, 1,5-naphthyridine intermediates and miscellaneous precursors have been prepared and submitted for biologic testing.

The brunt of our synthetic studies for this year has been directed at the formation of derivatives of 4-amino-1,5-naphthyridine which incorporate the methoxy functionality in the 2-position of the 1,5-naphthyridine ring. The desired target structures would, therefore, be isosteric to the highly potent antimalarials, primaquine, pentaquine and pamaquine. In addition, both the 6-methyl (alkoxy) and the 8-methyl functionalities were desired since these substituents are known to enhance biologic activity in related 8-aminoquinoline structures. Accordingly, we have applied both a number of conventional techniques and our improved ENME-N-OXIDE procedure for the formation of a variety of the requisite key intermediates, e.g., the 6- and 8-substituted-2,4-dichloro-1,5-naphthyridines. We have now determined that the interaction of these key intermediates with methoxide has led to the indiscriminate attack at either the 2- or 4-position to afford both the 4-chloro-2-methoxy- and 2-chloro-4-methoxy-1,5-naphthyridines. While the formation of the latter intermediates was initially disconcerting, they have proven to be useful precursors for the formation of the equally desired 2-amino-4-methoxy-1,5-naphthyridines. The detailed results of all of our synthetic studies conducted this year are fully delineated in the text of this report.

While full biologic testing data are not yet available, results obtained for most of the target drugs submitted to WRAIR have disclosed no significant prophylactic activity in the lower dosage range (1.0 and 3.0 mg/kg). However, one of the target structures, 2-hydroxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine, has now proven to be curative in the Rhesus monkey screen at a dosage level of 10.0 mg/kg. In the therapeutic screen, only minimal biologic activity has been observed for the target structures tested to date. In addition, no biologic activity was observed for any of the sixty-four variously substituted intermediates or precursors which have also been tested in the therapeutic screen.

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1. SUMMARY

Interest in the 4-amino-1,5-naphthyridines as potential prophylactic antimalarial agents has been generated by the structural similarity of this ring system to both the 4- and 8-aminoquinolines. In our synthetic studies for this year, we sought to expand upon the derivatives of 4-amino-1,5-naphthyridine which are currently available in an effort to secure an optimal prophylactic antimalarial drug. Accordingly, as a result of our synthetic efforts a total of sixty-one compounds comprising a variety of target structures, 1,5-naphthyridine intermediates and miscellaneous precursors have been prepared and submitted for biologic testing.

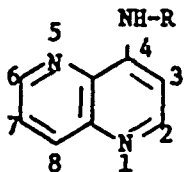
The brunt of our synthetic studies for this year has been directed at the formation of derivatives of 4-amino-1,5-naphthyridine which incorporate the methoxy functionality in the 2-position of the 1,5-naphthyridine ring. The desired target structures would, therefore, be isosteric to the highly potent antimalarials, primaquine, pentaquine and pamaquine. In addition, both the 6-methyl (alkoxy) and the 8-methyl functionalities were desired since these substituents are known to enhance biologic activity in related 8-aminoquinoline structures. Accordingly, we have applied both a number of conventional techniques and our improvised EMME-N-OXIDE procedure for the formation of a variety of the requisite key intermediates, e.g., the 6- and 8-substituted-2,4-dichloro-1,5-naphthyridines. We have now determined that the interaction of these key intermediates with methoxide has led to the indiscriminate attack at either the 2- or 4-position to afford both the 4-chloro-2-methoxy- and 2-chloro-4-methoxy-1,5-naphthyridines. While the formation of the latter intermediates was initially disconcerting, they have proven to be useful precursors for the formation of the equally desired 2-amino-4-methoxy-1,5-naphthyridines. The detailed results of all of our synthetic studies conducted this year are fully delineated in the text of this report.

While full biologic testing data are not yet available, results obtained for most of the target drugs submitted to WRAIR have disclosed no significant prophylactic activity in the lower dosage range (1.0 and 3.0 mg/kg). However, one of the target structures, 2-hydroxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine, has now proven to be curative in the Rhesus monkey screen at a dosage level of 10.0 mg/kg. In the therapeutic screen, only minimal biologic activity has been observed for the target structures tested to date. In addition, no biologic activity was observed for any of the sixty-four variously substituted intermediates or precursors which have also been tested in the therapeutic screen.

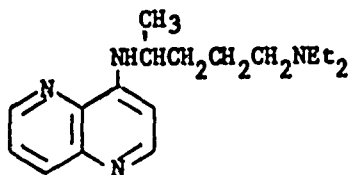
2. INTRODUCTION

The drugs presently available for the treatment of malaria suffer from two serious deficiencies. First, no single agent is suitable for all purposes. Secondly, drug resistant strains of the parasite have evolved in the early 1960's. Clearly, further developments in drug design must lead to agents which possess pharmacologic and chemotherapeutic properties which are superior to those presently available. The goals of new synthetic efforts must be directed toward the development of agents which exhibit broad activity against all life cycles of the parasite. In addition, they should possess high potency, low toxicity, and a long duration of activity. Ideally, a prophylactic drug is sought for the recently encountered drug resistant strains of the malaria parasite.

With all of the above in mind, it is our contention that certain 4-amino-1,5-naphthyridines,



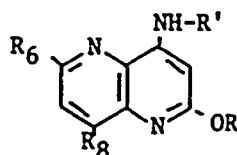
should possess the desired prophylactic characteristics. Quinine, a classic example of a specific chemotherapeutic agent, incorporates a quinoline ring as a basic structural fragment. The quinoline nucleus has, therefore, served as a template for biochemists in the design of a wide array of candidate antimalarial drugs. Of the many substituent variations effected upon the quinoline nucleus, the 4-amino and 8-amino substituted analogs have exhibited the greatest activity (1). In general, the 4-aminoquinolines, e.g., chloroquine, are schizontocidal agents which act at the asexual erythrocytic life cycle of the malaria parasite. By contrast, the 8-aminoquinolines, as typified by pamaquine, are gametocytocidal drugs which act against the secondary exoerythrocytic stages and thereby destroy the sexual forms of the human malaria parasite (2). Derivatives of the 4-amino-1,5-naphthyridines should, therefore, exhibit an enhanced antimalarial activity, since they are isosteres of both the 4- and 8-aminoquinolines. This supposition has been confirmed by an early report in the literature that 4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine,



was found to exhibit an antimalarial activity comparable to quinine itself (3,4). Moreover, recent reports in the literature have disclosed significant antimalarial activity for the 4-amino-1,5-naphthyridines which are substituted with alkoxy groups in both the 2- and 6-positions (2,5). In our research, we sought to expand upon the derivatives of 4-amino-1,5-naphthyridine currently available in an effort to produce an optimum drug. The results of our synthetic studies for this year are fully discussed in the text of this report.

3. SYNTHESIS-RESULTS AND DISCUSSION

In this, the second year of our research, we have primarily sought the synthesis of derivatives of 4-amino-1,5-naphthyridine which exhibit the following generalized structure.



R = CH₃, H

R' = $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{CH}(\text{CH}_2)_3 \text{N}^+\text{Et}_2 \end{array}$ (Pamaquine Side Chain)

R₆ = CH₃, OR; R₈ = H

$\begin{array}{c} \text{CH}_3 \\ | \\ -\text{CH}(\text{CH}_2)_3 \text{NH}_2 \end{array}$ (Primaquine Side Chain)

R₆ = H, OR; R₈ = CH₃

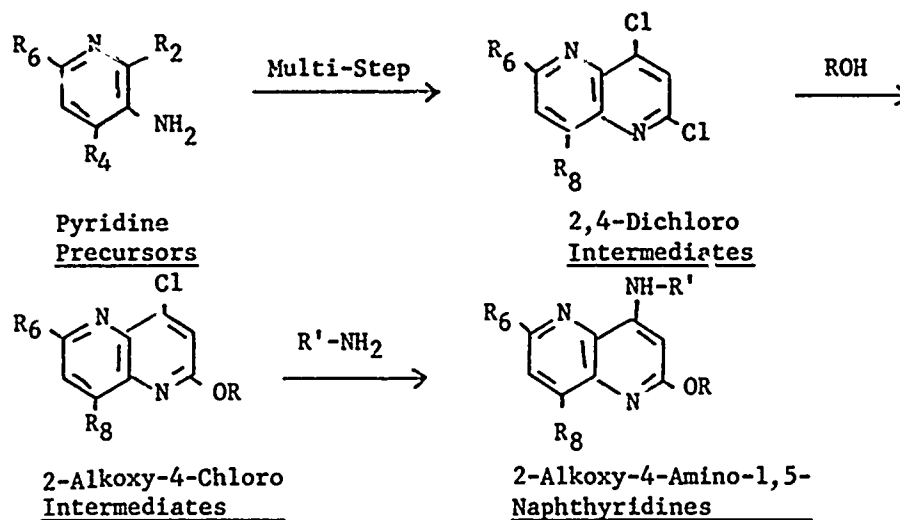
$-(\text{CH}_2)_5 \text{NHCH}(\text{CH}_3)_2$ (Pentaquine Side Chain)

The biologic rationale and substantiating data upon which this choice was made has been fully documented in our research proposal (6). In essence, these 4-amino-1,5-naphthyridines are the "5-aza" isosteres of highly active 8-aminoquinolines. As such, they are also isosteric to the 4-aminoquinoline drugs, and they should therefore possess enhanced activity characteristics as compared to either of these proven classes of antimalarials. The ring substituents and their sites of attachment have been dictated by comparison of the desired 4-amino-1,5-naphthyridines with their active 8-aminoquinoline counterparts. Alkoxy and hydroxy groups were included in the 2-position since it is the current opinion of WRAIR personnel that oxygenation meta to the exocyclic amino group is a prerequisite for the antimalarial activity in the 1,5-naphthyridines which are structurally related to the 8-aminoquinolines (7). The inclusion of the 6- and 8-methyl groups were sought since the 2-methyl- and 4-methylprimaquine antimalarials are currently the most active 8-aminoquinolines in the prophylactic screen (8). Finally, 6-alkoxy substituent were chosen since it is known that this grouping imparts improved therapeutic activity to the 4-amino-1,5-naphthyridines (5). The latter choice is also supported by Blanton's report that the inclusion of a benzyloxy group in the 2-position of primaquine reduces toxicity while maintaining biologic activity (9). This is in agreement with Holmes' original speculation concerning the advantage of deliberately introducing oxygen functionality into the 2-position of quinoline antimalarials (10).

An identical reaction sequence was employed this year for the formation of each of the desired target structures. The basic features of this overall synthetic route to the variously substituted 4-amino-1,5-naphthyridines are illustrated in Scheme 1.

Scheme 1

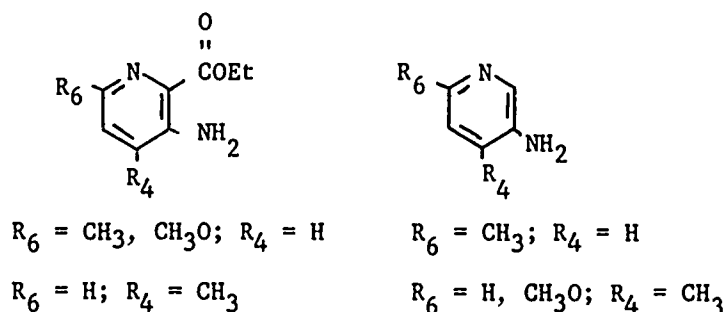
General Synthetic Route to Target Structures



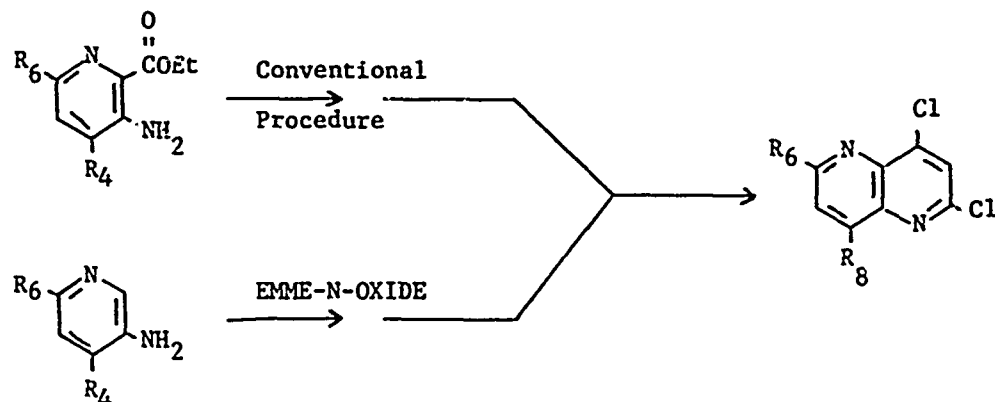
In the following subsections (3.1 through 3.4) we have included a complete description of the procedures used for: (1) the synthesis of the pyridine precursors illustrated in Scheme 1; (2) the synthesis of the 2,4-dichloro-1,5-naphthyridine intermediates; (3) the synthesis of the 2-alkoxy-4-chloro-1,5-naphthyridine intermediates; and finally, (4) the synthesis of the desired 2-alkoxy-4-amino-1,5-naphthyridine target structures. Also, in Section 3.5 we have included a description of the preparative chemistry of several miscellaneous intermediates whose syntheses were also explored this year.

3.1 Synthesis of Pyridine Precursors

The pyridine precursors whose syntheses were sought this year were of two basic types. These have included variously substituted 3-aminopyridines and 3-aminopyridines.



As shown below, these precursors were used for the formation of the 2,4-dichloro-1,5-naphthyridine key intermediates via two independent synthetic routes.



The first synthetic route depicted above is based upon the conventional von Niementowski synthetic sequence as has been widely applied for the formation of a variety of quinoline antimalarials (11). The second procedure is based upon our improvised EMME-N-OXIDE reaction sequence, the preliminary details of which were originally reported last year (12).

In the two subsections below, we have described the detailed procedures used for the formation of both the 3-aminopicolinate and 3-aminopyridine precursors which were synthesized this year.

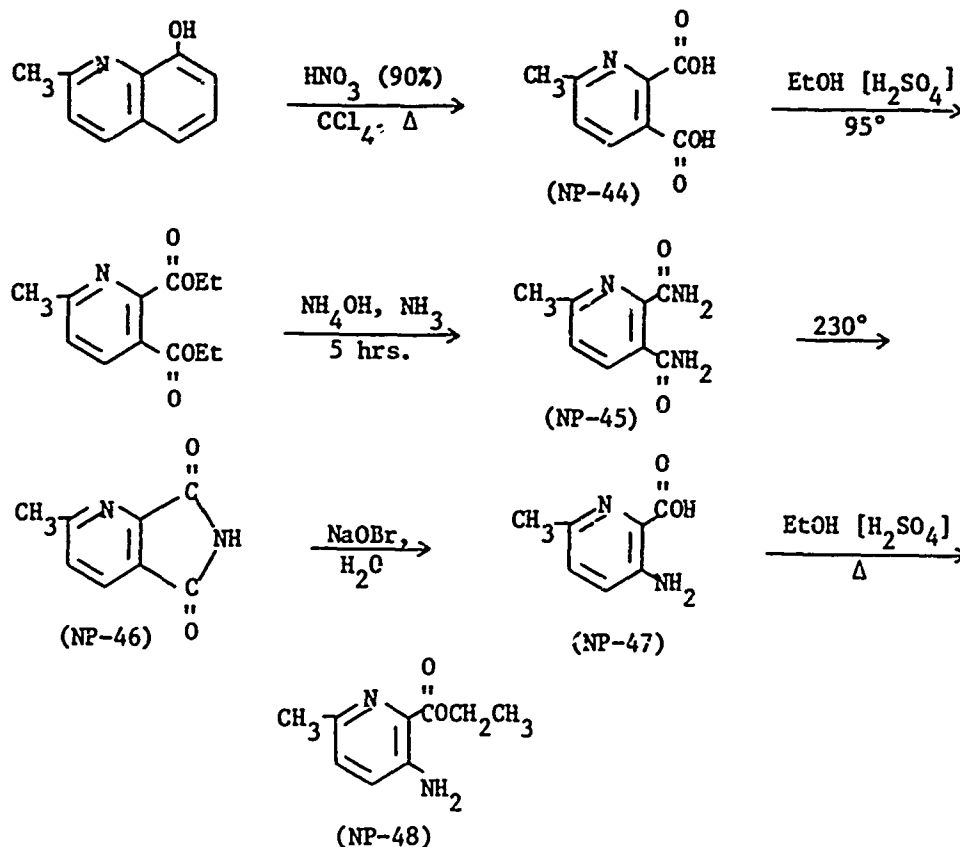
3.1.1 Formation of 3-Aminopicolinates

The title precursors which have been characterized to date have primarily included methyl groups in either the 4- or 6-position of the pyridine ring. A description of their preparative chemistry is included below, and the analytical data and physical constants for the precursors which were submitted to WRAIR are included in Table 1 at the end of this section.

The requisite precursor to the 6-methyl analogs, ethyl 3-amino-6-methylpicolinate, has not, to our knowledge, been reported in the literature. The synthetic route which was employed for the formation of this precursor is illustrated in Scheme 2.

Scheme 2

Preparation of Ethyl 3-Amino-6-Methylpicolinate



In general, each of the steps leading to the production of 3-amino-6-methylpicolinic acid in Scheme 2 have been reported in the literature (13, 14, 15). Accordingly, the benzo ring of 8-hydroxyquinaldine was first selectively oxidized employing fuming nitric acid (90%). While not reported in the original literature, we have found that the reaction mixture must be heated to 80-85° after the initial addition at 0-5°. If this additional heating is not performed, the benzo ring is not cleaved and unreacted 8-hydroxyquinaldine is recovered exclusively. The analytically pure 6-methylquinolinic acid (NP-44) was then isolated from the reaction mixture by recrystallization from ethanol-ether. The infrared spectrum for this acid typically displayed only broad absorptions (Figure 1).

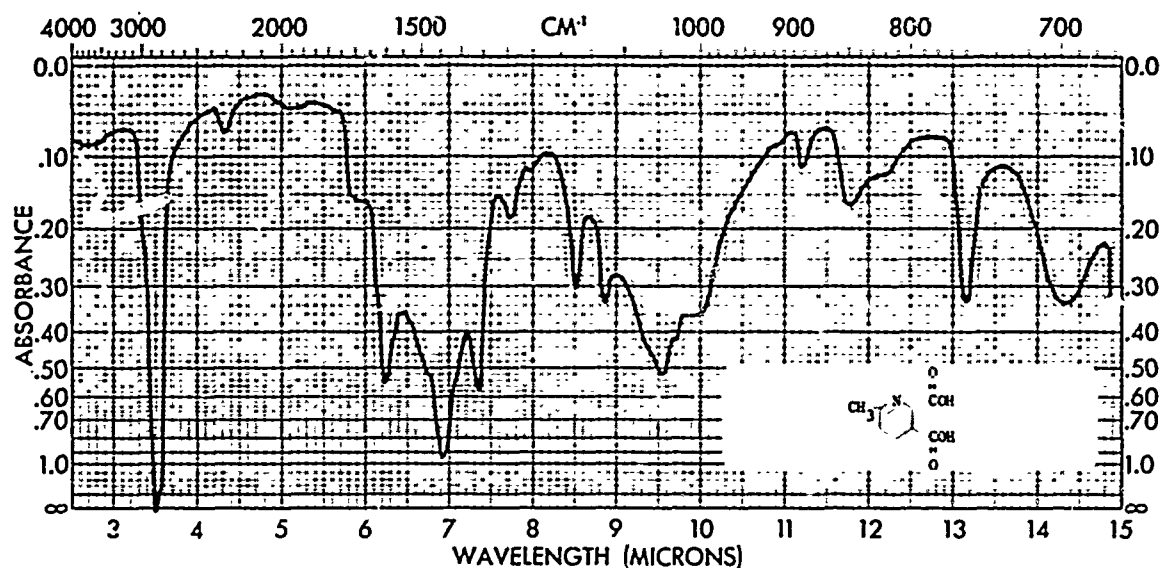


Figure 1. Infrared spectrum of 6-methylquinolinic acid (nujol mull).

The succeeding step of Scheme 2, esterification of the 6-methylquinolinic acid, was accomplished employing a 50:50 mixture of ethanol and concentrated sulfuric acid at 95-100°. The diester was not purified at this stage, but was reacted with gaseous ammonia in concentrated ammonium hydroxide to afford the bis-amide (NP-45). The pure bis-amide was obtained by recrystallization from methanol, and its infrared spectrum (Figure 2) clearly discloses the presence of two amide group absorptions near 6.0 μ .

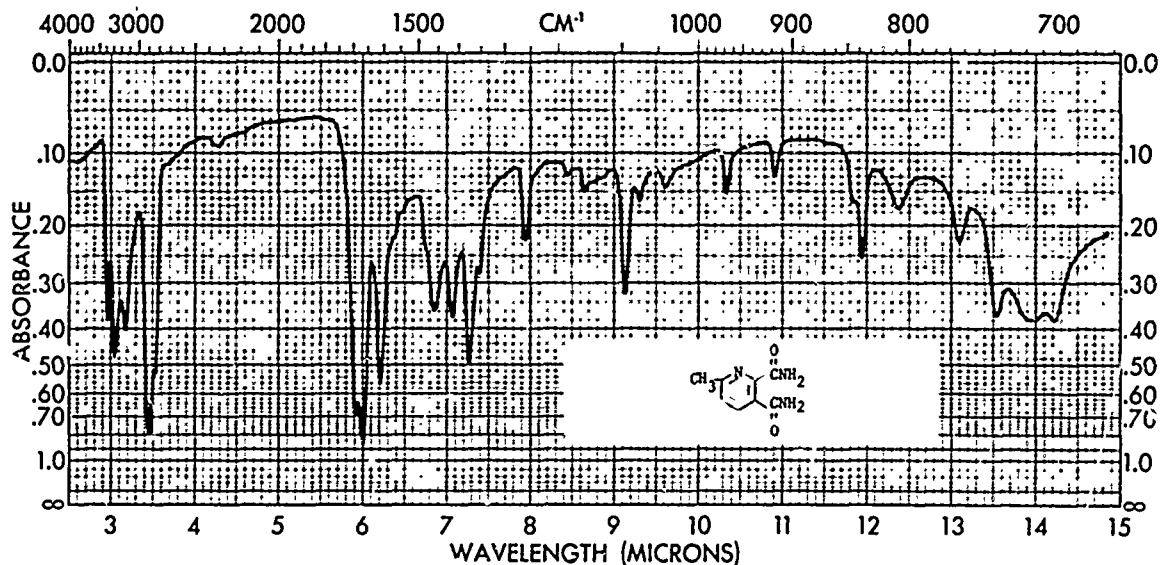


Figure 2. Infrared spectrum of 6-methylquinolindiamide (nujol mull).

The infrared spectrum for the pure, dry acid obtained after recrystallization from water (Figure 4), is consistent solely with a zwitterionic formulation in the solid state (16). Only a broad carboxylate absorption near 6.3μ is therefore observed.

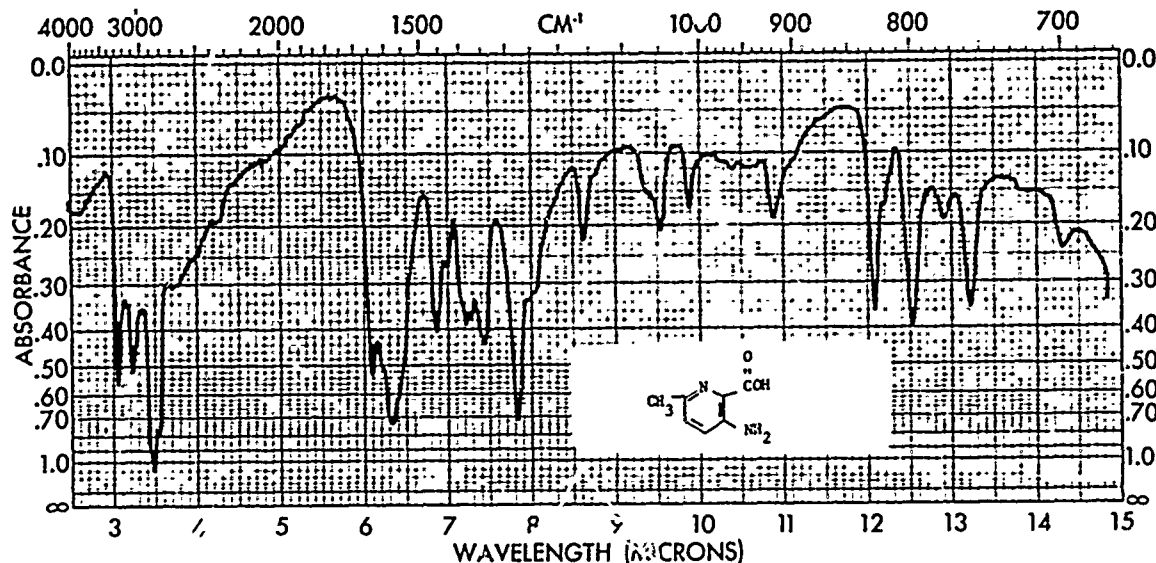
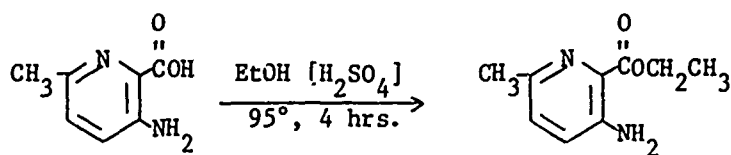


Figure 4. Infrared spectrum of 3-amino-6-methylpicolinic acid (nujol mull).

The final step of Scheme 2, esterification of the 3-amino-6-methylpicolinic acid, was conducted in a 50:50 weight percent mixture of concentrated sulfuric acid-ethanol at $95-100^\circ$ for four hours.



The product, ethyl 3-amino-6-methylpicolinate (NP-48), was isolated as a white solid after recrystallization from ether-heptane. Its infrared spectrum was consistent with the formulated structure, and its proton spectrum is reproduced in Figure 5. The 6-methyl singlet is present at 7.51τ , and the two ring protons are present, somewhat surprisingly, as a sharp singlet at 2.93τ . Evidently, the shielding effect of both the ring methyl group and the amino moiety are balanced. The H-4 and H-5 ring protons are therefore magnetically equivalent and no splitting is observed (17).

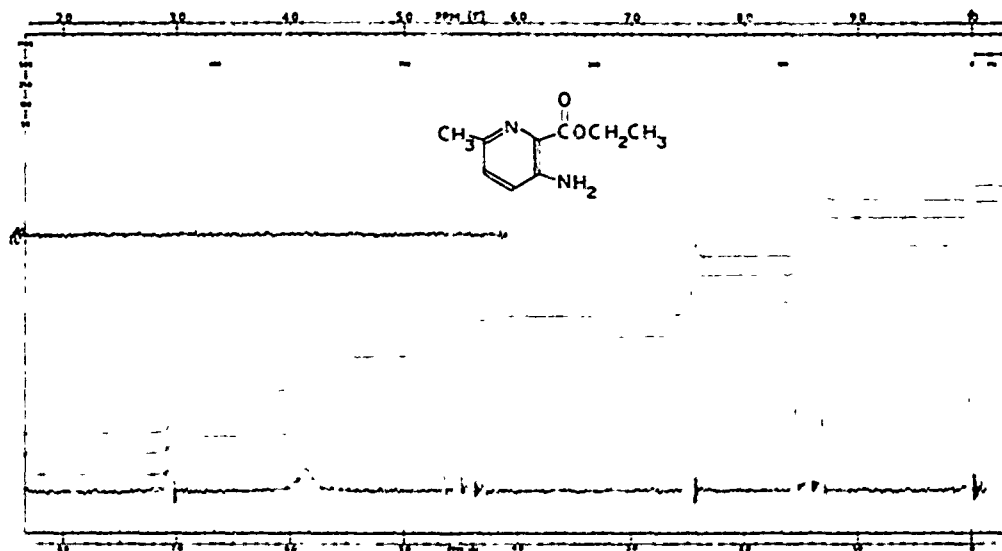
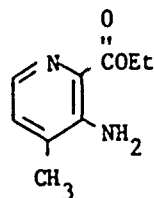


Figure 5. Proton spectrum of ethyl 3-amino-6-methylpicolinate (CDCl_3)

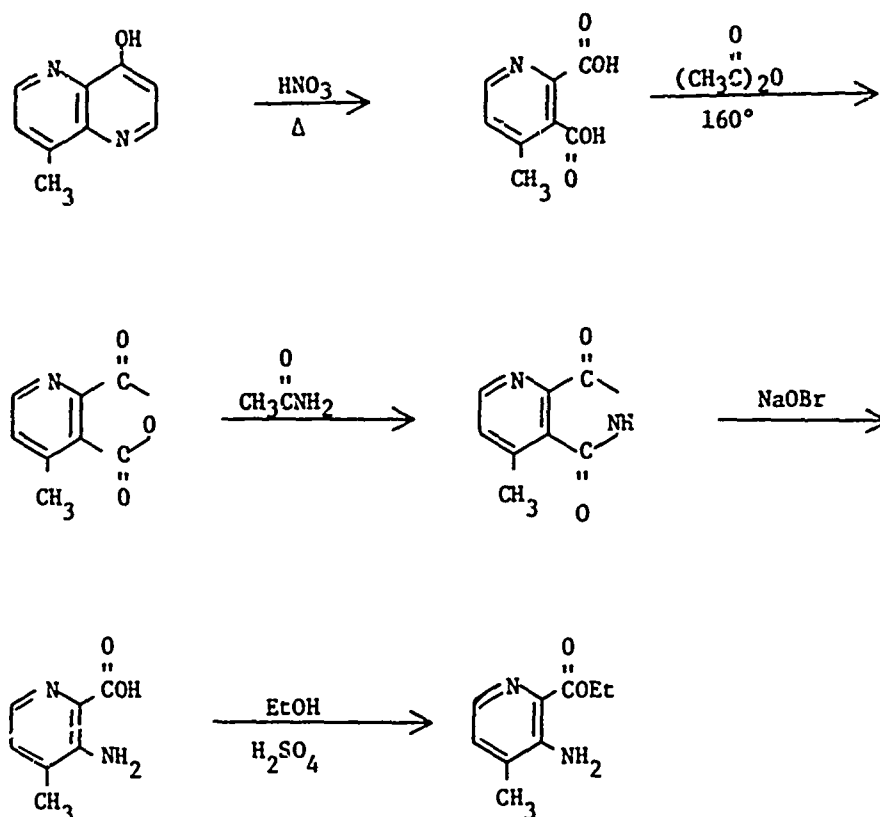
Our synthesis of the desired 8-methyl analogs of 4-amino-1,5-naphthyridine has required the isolation of ethyl 3-amino-4-methylpicolinate.



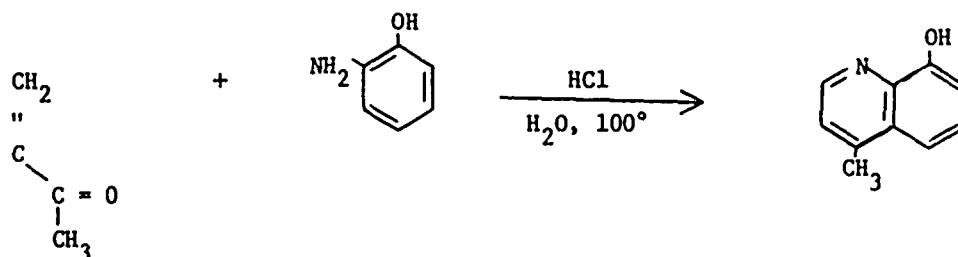
The overall route which we are currently employing for the formation of this precursor is illustrated in Scheme 3.

Scheme 3

Preparation of Ethyl 3-Amino-4-Methylpicolinate



All precursors which have been characterized to date in accord with Scheme 3 are also included in Table 1 at the end of this section. The starting material for Scheme 3, 8-hydroxy-4-methylquinoline, while commercially available (18) was grossly impure. We have, therefore scaled up its synthesis via the Doebner-Miller techniques as reported by Phillips (19).



No effective oxidizing agent could be found for this reaction which probably accounts for the low yield of only 20%. For the work-up of this reaction, we followed Phillips report followed by prolonged steam distillation of the basified reaction mixture as recently reported by Blank (20). The infrared spectrum for the pure 8-hydroxy-4-methylquinoline is reproduced in Figure 6.

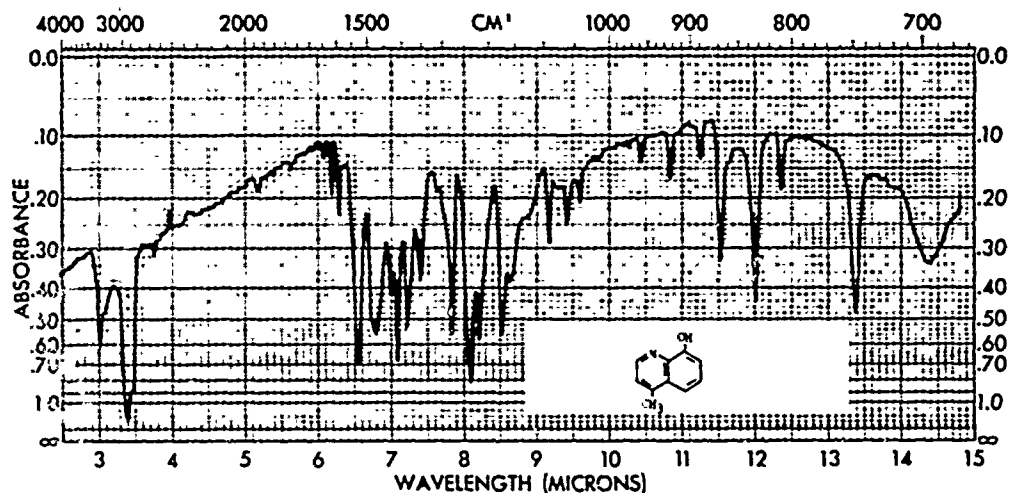


Figure 6. Infrared spectrum of 8-hydroxy-4-methylquinoline (nujol mull).

Oxidation of the benzo ring of 8-hydroxy-4-methylquinoline was then conducted by the improved procedure as reported by Blank (20). The addition of the solid 8-hydroxy-4-methylquinoline into the fuming nitric acid at 10° was very exothermic. After heating to 85° to drive off the nitrogen oxide fumes, the water was removed, and the residue was recrystallized from ethanol-ether (or water) to afford the pure acid in 70% yield. The infrared spectrum of the pure acid (NP-64) is reproduced in Figure 7.

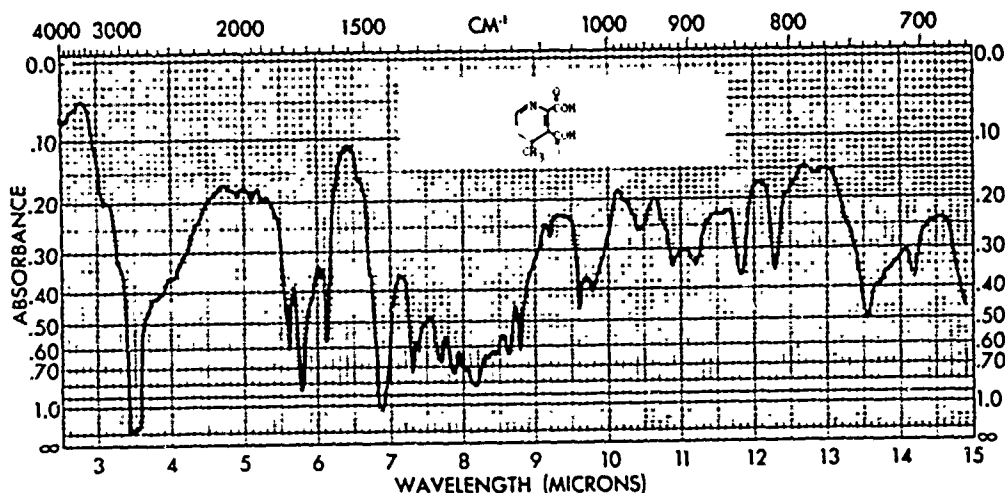
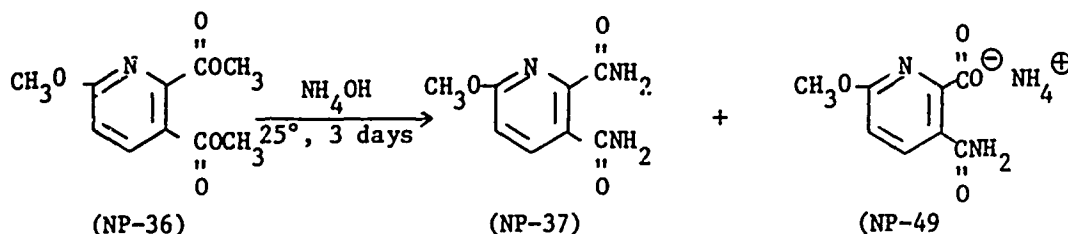


Figure 7. Infrared spectrum of 4-methylquinolinic acid (nujol mull).

The succeeding steps of Scheme 3, up to the formation of the 3-amino-4-methylpicolinic acid (NP-69), were essentially conducted as Sucharda has described for the preparation of the unsubstituted 3-amino-picolinic acid (21). The intermediary 4-methylquinolinic anhydride (NP-67) exhibited a melting point virtually identical to that reported in the literature (22). The 4-methylquinolinimide (NP-68) was isolated in a crude yield of 46% via this procedure, and exhibited a melting point approximately ten degrees higher than the reported value (20) after recrystallization from glacial acetic acid. Conversion of the imide to the 3-amino-4-methylpicolinic acid (NP-69) via the Hofmann degradation technique afforded the crude acid in 44% yield. The crude amino acid was contaminated with a small amount of the isomeric 2-amino-4-methylnicotinic acid as attested by a minor absorption near 5.9μ in the infrared. After recrystallization from methanol, the pure acid was obtained with a strong absorption near 6.1μ . The analytically pure 3-amino-4-methylpicolinic acid (NP-69) as obtained from methanol again exhibited a melting point roughly 10° higher than that previously reported (20). At the present time, we are in the process of conducting the last step as illustrated in Scheme 3. The results of these investigations will be related in subsequent reports.

The last two precursors listed in Table 1, NP-49 and NP-50, were prepared as fully described in the experimental section. Ammonium 3-carboxamido-6-methoxypicolinate, NP-49, was isolated as a by-product in the scale-up of precursors to the 2,6-dialkoxy-4-amino-1,5-naphthyridines.



While the formation of NP-49 in the scale-up was disconcerting at first, we have noted that its pyrolysis also led to the formation of 6-methoxyquinolinimide (NP-38).

Table 1
Precursors to Substituted 3-Aminopicolinates

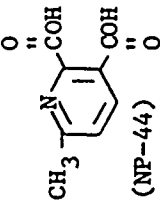
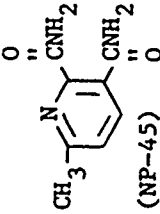
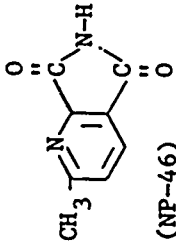
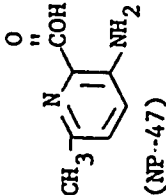
Structure	M.P., °C	Elemental Analysis			Theory Found
		C	H	N	
 (NP-44)	174-176	53.04 52.80	3.90 3.85	7.73 7.90	
 (NP-45)	241-244	53.63 53.64	5.06 5.20	23.45 23.65	
 (NP-46)	249-250	59.25 59.03	3.73 3.84	17.28 17.38	
 (NP-47)	210-212	55.25 55.02	5.30 5.33	18.42 18.38	

Table 1 (Cont'd)
Precursors to Substituted 3-Aminopicolinates

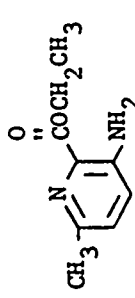
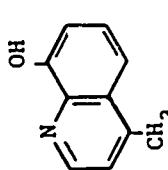
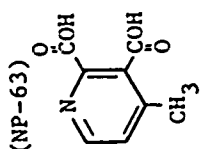
Structure	M.P., °C	Elemental Analysis			Theory Found
		C	H	N	
 (NP-48)	169-170	59.98 59.96	6.71 6.74	15.55 15.55	
 (NP-63)	140-141	75.45 75.45	5.70 5.83	8.80 8.70	
 (NP-64)	189-191	53.04 52.78	3.99 3.93	7.73 7.47	

Table 1 (Cont'd)
Precursors to Substituted 3-Aminopicolinates

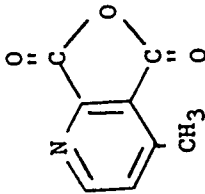
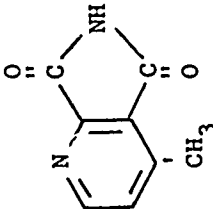
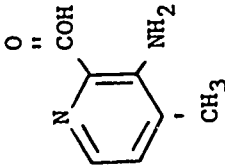
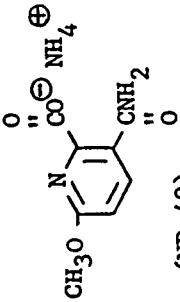
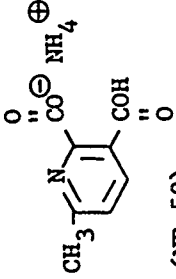
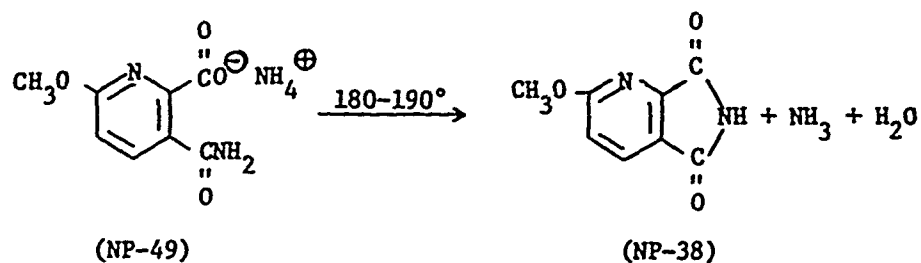
Structure	M.P., °C	Elemental Analysis			Theory Found
		C	H	N	
 (NP-67)	163-164	58.90 58.79	3.09 2.97	8.59 8.41	
 (NP-68)	248-250	59.25 59.43	3.73 3.61	17.28 17.47	
 (NP-69)	237-238	55.25 55.04	5.30 5.25	18.42 18.39	

Table 1 (Cont'd)

Precursors to Substituted 3-Aminopicolinates

Structure	M.P., °C	Elemental Analysis			Theory Found
		C	H	N	
 (NP-49)	190-191	45.07 45.27	5.20 5.17	19.71 19.08	
 (NP-50)	194-197	48.48 48.36	5.08 5.08	14.14 14.00	



Not only was the yield of NP-38 quantitative, but the temperature required for this conversion was lower than starting from the diamide (NP-37). We therefore prepared ammonium 6-methylquinolinate, NP-50, in the hopes that its pyrolysis would lead to the formation of 6-methylquinolinimide, NP-46, via a more facile procedure than we have outlined earlier in this section. However, the pyrolysis of NP-50 was unrewarding (tar formation). We have therefore abandoned this alternative route.

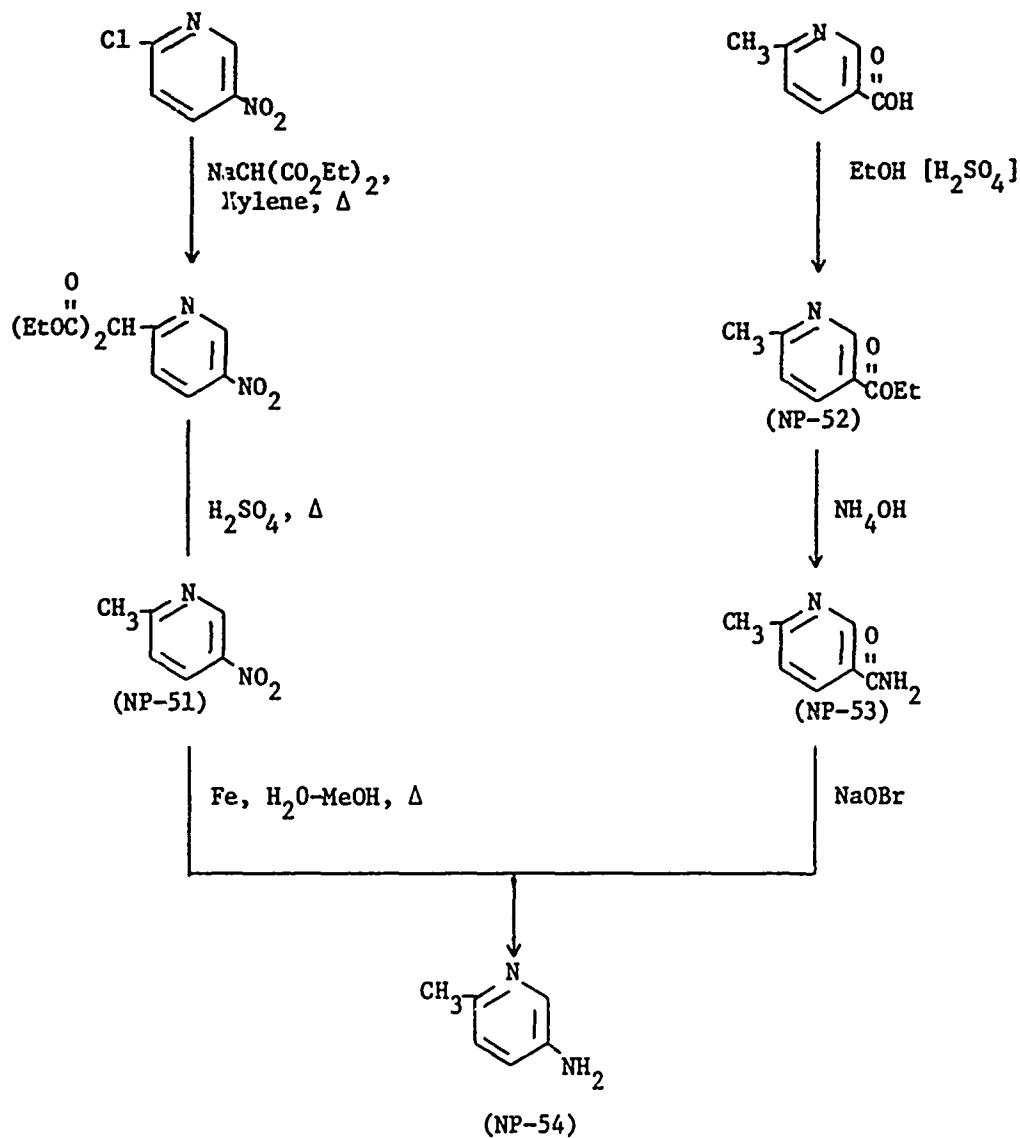
3.1.2 Formation of 3-Aminopyridines

The 3-aminopyridine precursors which were prepared this year were utilized for the EMME-N-OXIDE route to the target structures. The 3-aminopyridines of interest have included the 4- and 6-methyl groups, and a description of their preparation chemistry is included below. The analytical data and physical constants for all precursors characterized in conjunction with these studies are included in Table 2 at the end of this section.

The synthetic routes available for the formation of 5-amino-2-picoline are illustrated in Scheme 4.

Scheme 4

Preparation of 5-Amino-2-Picoline



The first route (up to the formation of NP-51) was recently reported by Achremowicz (23). The iron-acetic acid reduction of this precursor, by analogy to Friedman's general procedure (24), could only be effected in the presence of an excess of iron and acetic acid (see Experimental). Nevertheless, this route was preferred over the second procedure (25). The precursors which were prepared and characterized via either of these two routes are included in Table 2 at the end of this section. Also, the proton spectra for NP-52 and NP-54 are reproduced in Figures 8 and 9 respectively.

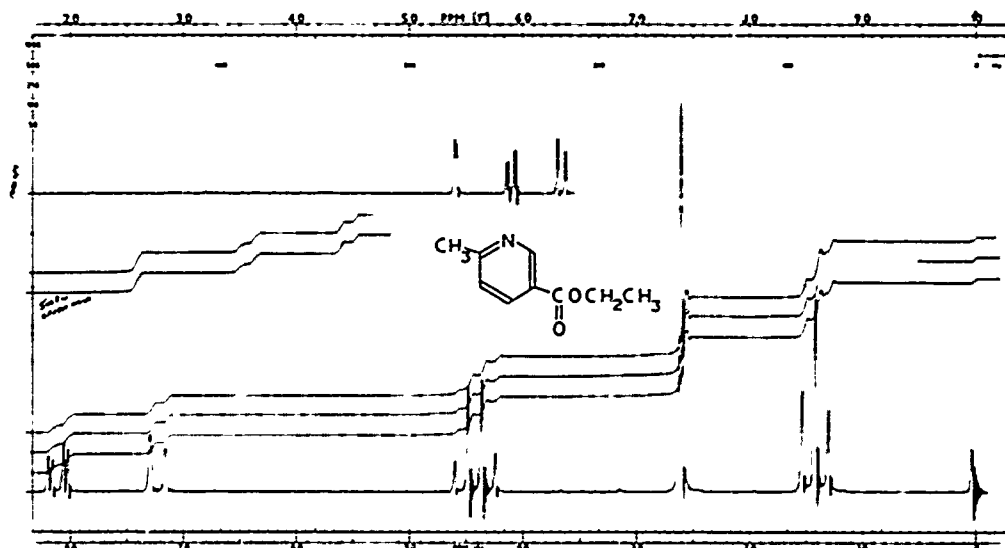


Figure 8. Proton spectrum of ethyl 6-methylnicotinate (neat).

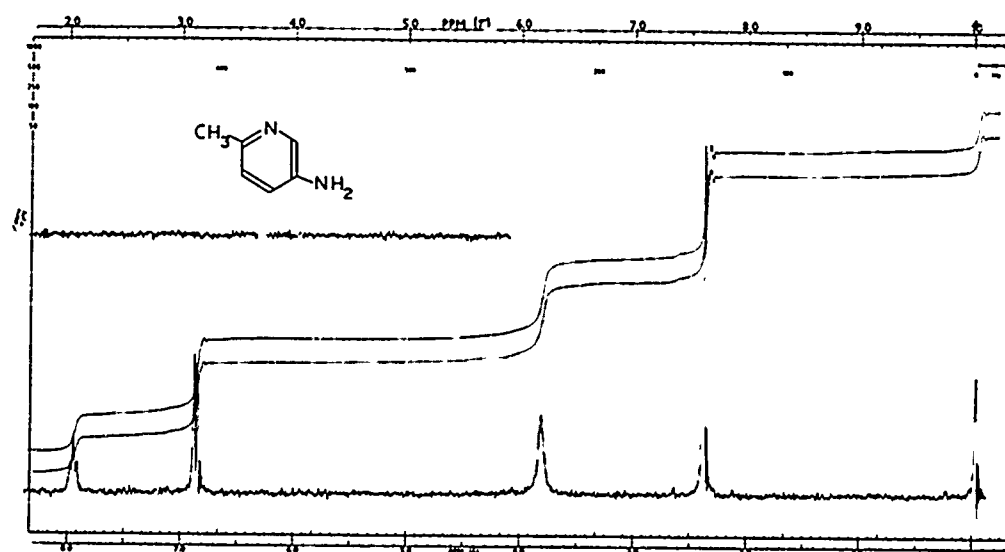
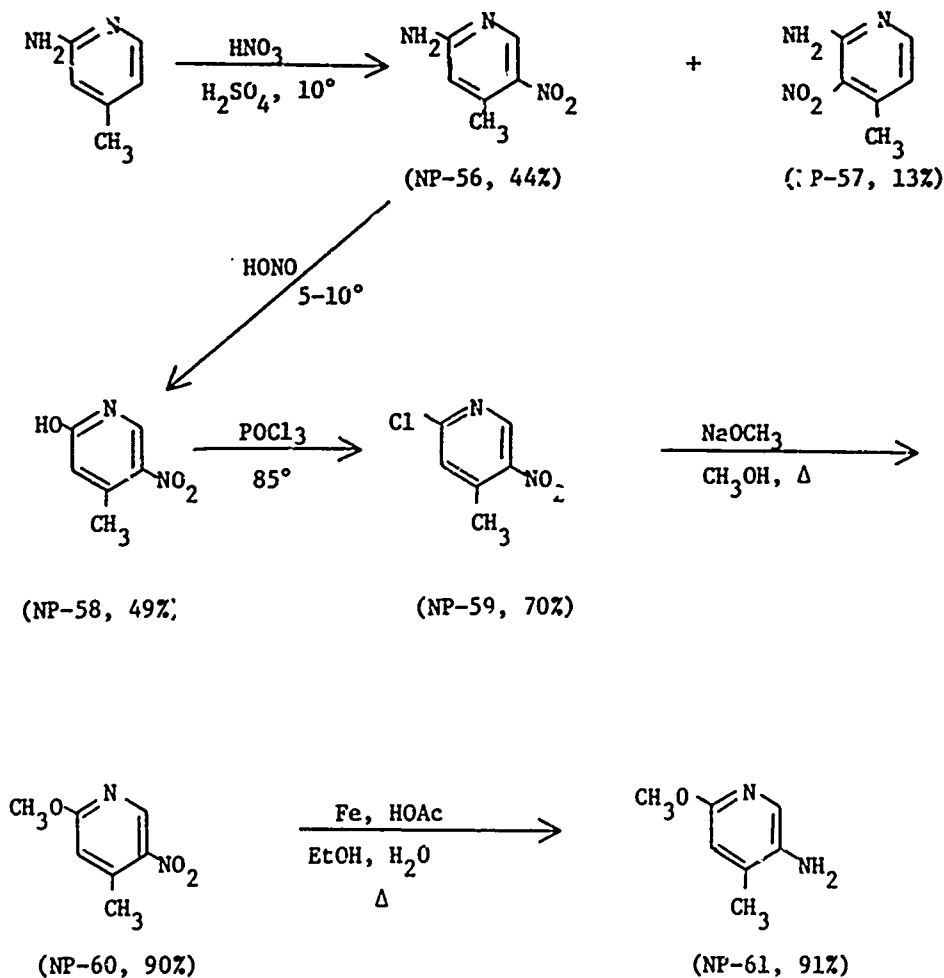


Figure 9. Proton spectrum of 5-amino-2-picoline (CDCl_3).

The procedures utilized for the formation of 5-amino-2-methoxy-4-picoline (NP-61) are outlined in Scheme 5.

Scheme 5

Preparation of 5-Amino-2-Methoxy-4-Picoline



Each of the steps illustrated in Scheme 5 have been previously reported in the literature via a number of investigators. The particular procedure which was followed at each step was chosen for the sake of convenience. The initial step, nitration of the commercially available 2-amino-4-picoline, was performed as Baumgarten has described (26). The crude mixture of the 2-amino-5-nitro- and 2-amino-3-nitro-4-picolines was isolated as a tan solid in 92% yield. While Seide has reported the use of steam distillation to separate the more volatile 3-nitro isomer from the non-volatile 5-nitro isomer (27, see Experimental), we found that the distillation had to be conducted for a considerable length of time. Since

it was necessary to run this reaction many times, we have now found it to be more convenient to simply triturate the crude mixture with hot ethanol. The desired 5-nitro isomer was then isolated by filtration of the hot ethanol solution. The infrared spectra for the pure 2-amino-5-nitro-4-picoline and 2-amino-3-nitro-4-picoline are reproduced in Figures 10 and 11 respectively.

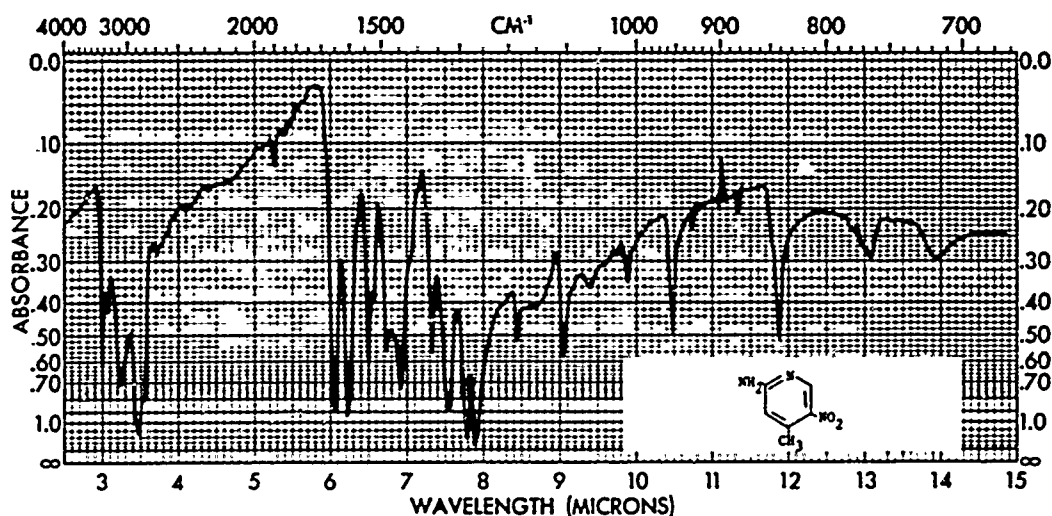


Figure 10. Infrared spectrum of 2-amino-5-nitro-4-picoline (nujol mull).

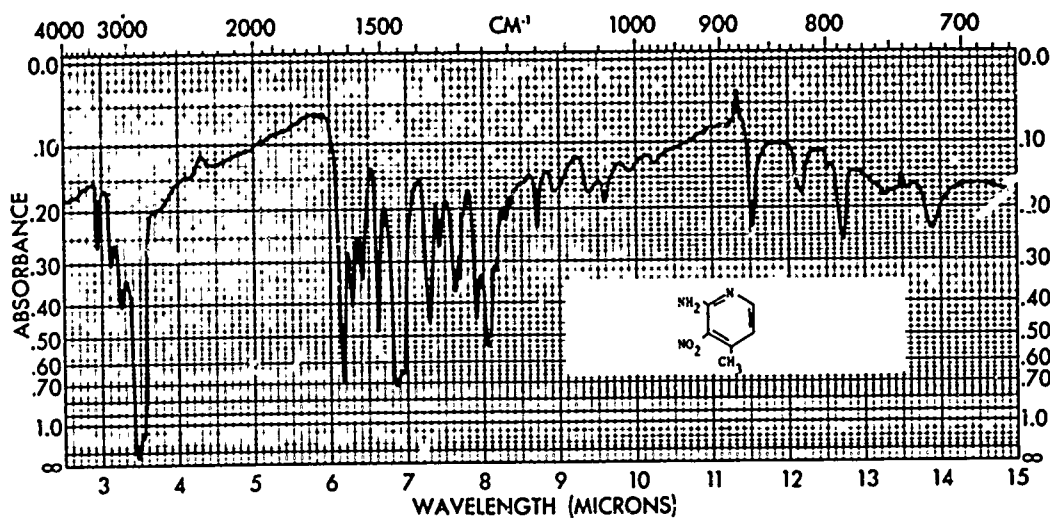


Figure 11. Infrared spectrum of 2-amino-3-nitro-4-picoline (nujol mull).

The succeeding step of Scheme 5, diazotization of NP-56 and hydrolysis, was performed exactly as Baumgarten has described (26). The crude 2-hydroxy-5-nitro-4-picoline was isolated in 49% yield. Its infrared spectrum was identical to the purified sample (Figure 12).

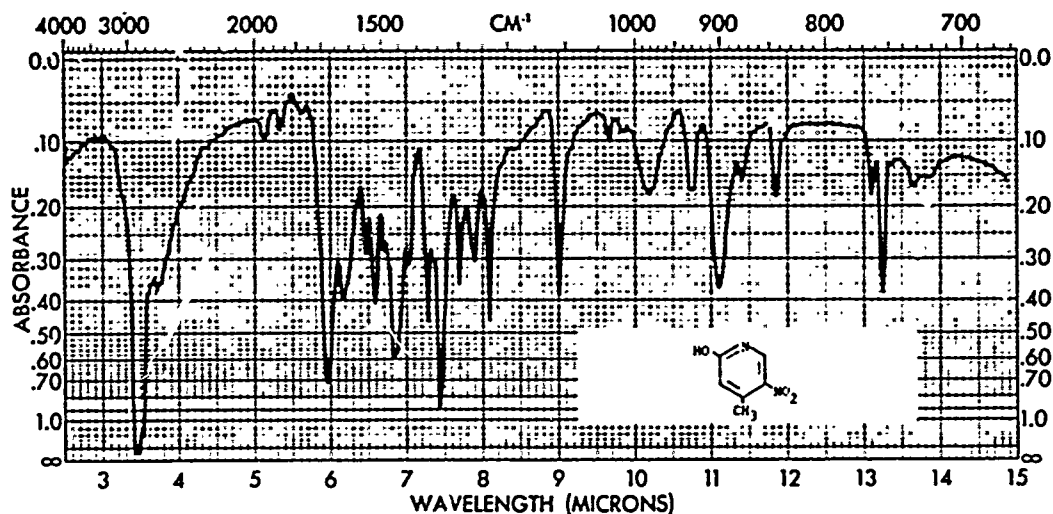


Figure 12. Infrared spectrum of 2-hydroxy-5-nitro-4-picoline (nujol mull).

Conversion of NP-58 into the 2-chloro-5-nitro-4-picoline (NP-59) was performed as Roe and Seligman have described (28). Inclusion of the 6-methoxy group (NP-60), and reduction of the nitro group to afford the desired 5-amino-2-methoxy-4-picoline (NP-61) were performed as Goldberg has reported (29). The proton spectrum of NP-61 is reproduced in Figure 13.

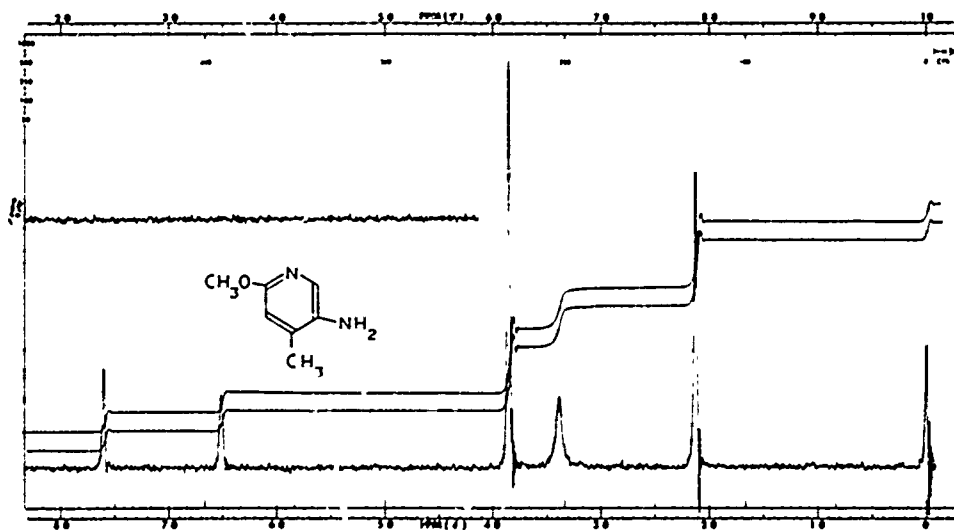
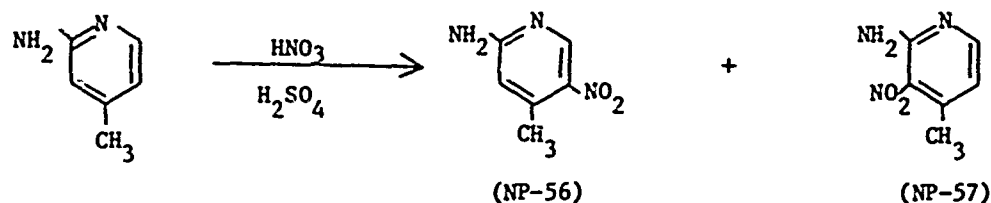


Figure 13. Proton spectrum of 5-amino-2-methoxy-4-picoline (CDCl₃).

As an alternative route to the 8-methyl target structures, we are presently employing the following procedure. It was mentioned earlier in this section that the nitration of 2-amino-4-picoline affords a mixture of both the 3-nitro and 5-nitro isomers.



We have described the use of the 5-nitro isomer (NP-56) for the preparation of precursors to the 6-alkoxy-8-methyl target structures. Rather than discard the 3-nitro by-product produced in this reaction (NP-57), we are currently utilizing this precursor as a route to 3-amino-4-picoline as Roe and Seligman have described (28). This amine may then be used to prepare the target 8-methyl analogs via our EMME-N-OXIDE route. The precursors secured to date are the 2-hydroxy-3-nitro-4-picoline (NP-65), and the 2-chloro-3-nitro-4-picoline (NP-66). The analytical data for both of these precursors are included in Table 2. The clean separation of isomers is attested by the infrared spectrum of the 2-hydroxy-3-nitro-4-picoline (Figure 14, compare with the infrared spectrum of the 5-nitro isomer, Figure 12).

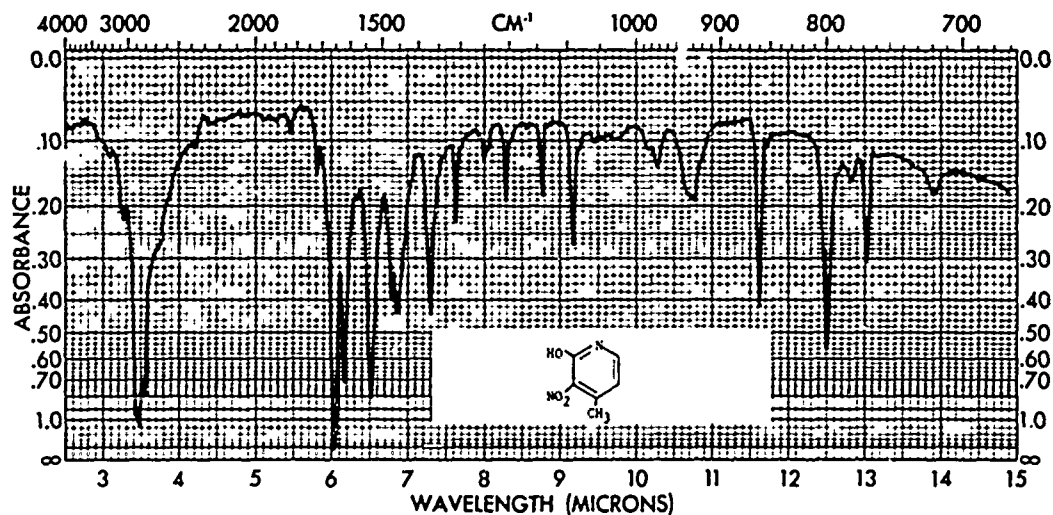


Figure 14. Infrared spectrum of 2-hydroxy-3-nitro-4-picoline (nujol mull).

The succeeding steps in this synthetic procedure are currently under investigation and will be reported at a later date.

Table 2

Precursors to Substituted 3-Aminopyridines

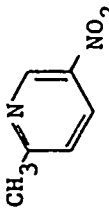
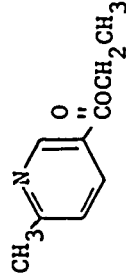
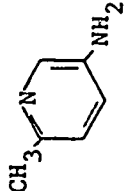
Structure	M.P., °C B.P., °C (mm)	Elemental Analysis			Theory Found
		C	H	N	
 (NP-51)	109-111	52.17 51.84	4.38 4.32	20.29 20.07	
 (NP-52)	119-120 (16.0 mm)	65.43 65.64	6.71 6.74	8.48 8.77	
 (NP-53)	206-207	61.75 61.81	5.92 5.86	20.58 19.99	
 (NP-54)	95-97	66.64 66.70	7.45 7.38	25.91 25.73	

Table 2 (Cont'd)
Precursors to Substituted 3-Aminopyridines

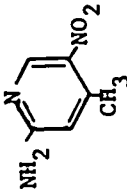
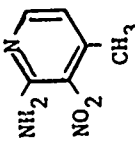
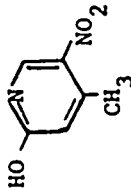
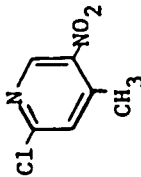
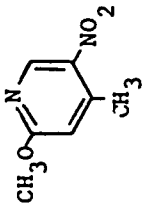
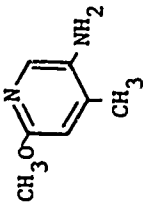
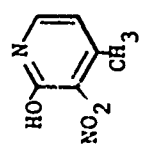
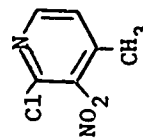
Structure	M.P., °C B.P., °C (mm)	Elemental Analysis			Theory Found
		C	H	N	
	229-230	47.05 47.05	4.61 4.59	27.44 27.03	
(NP-56)					
	139-139.5°	47.05 47.07	4.61 4.72	27.44 27.07	
(NP-57)					
	189-190°	46.75 46.46	3.93 4.04	18.18 17.96	
(NP-58)					
	114-116 (6.0)	41.75 41.64	2.92 3.01	16.24 16.10	
(NP-59)					

Table 2 (Cont'd)
Precursors to Substituted 3-Aminopyridines

Structure	M.P., °C B.P., °C (mm)	Elemental Analysis			Theory Found
		C	H	N	
 (NP-60)	79-80	50.00 49.59	4.79 4.79	16.66 16.38	
 (NP-61)	93-95	60.85 60.93	7.30 7.10	20.28 20.37	
 (NP-65)	237-239	46.75 46.71	3.93 3.98	18.18 18.17	
 (NP-66)	47-48	41.75 41.81	2.92 3.01	16.24 16.17	

3.2 Synthesis of the 2,4-Dichloro-1,5-Naphthyridine Intermediates

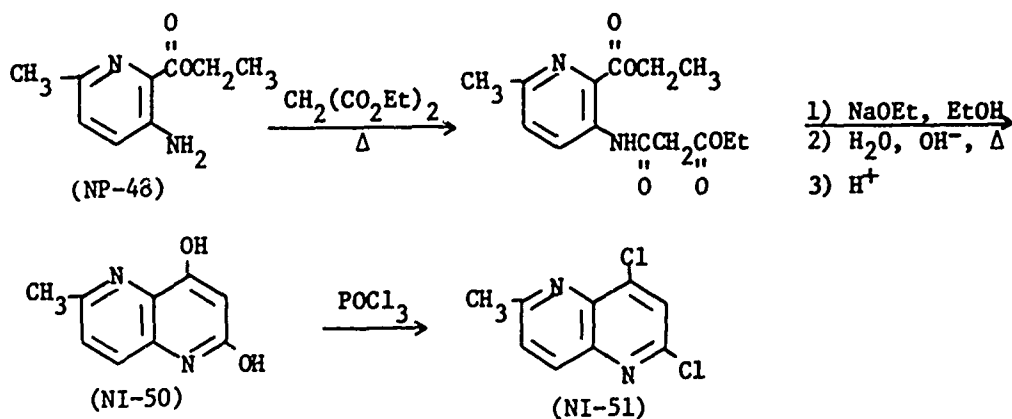
As related earlier in this report, two synthetic options were available to us for the formation of the title key intermediates. The first procedure is based upon the conventional von Niementowski synthetic route (11) as has been successfully been applied for the formation of the unsubstituted 2,4-dichloro-1,5-naphthyridine (30). The second procedure is based upon our improvised EMME-N-OXIDE route, the preliminary details of which were reported last year (12). The synthetic progress attained this year via either of these two routes is fully explained in Sections 3.2.1 and 3.2.2 respectively.

3.2.1 Conventional Synthetic Route to 2,4-Dichloro-1,5-Naphthyridines

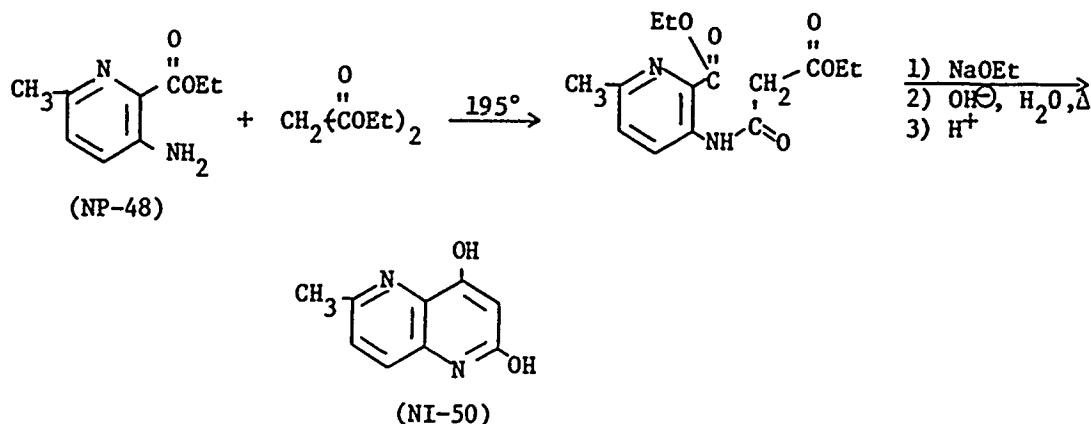
This year, we utilized the conventional technique only for the formation of the 6-methyl-2,4-dichloro-1,5-naphthyridine (NI-51). Starting from our preformed ethyl 3-amino-6-methylpicolinate (NP-48), the overall synthetic route to NI-51 is illustrated in Scheme 6.

Scheme 6

Preparation of 2,4-Dichloro-6-Methyl-1,5-Naphthyridine



The naphthyridine intermediates depicted in Scheme 6 which have been fully characterized this year are included in Table 3 at the end of this section along with their physical constants and full analytical data. The formation of 2,4-dihydroxy-6-methyl-1,5-naphthyridine, NI-50, was performed by analogy to the generalized von Niementowski synthetic procedure (11, 30).



The intermediary mono-amide was not isolated, but was directly subjected to a Dieckmann cyclization followed by decarboxylation. After acidification of the reaction mixture, the crude dihydroxy derivative, NI-50, was isolated as an off-white solid in 59% yield. The analytical sample was prepared by recrystallization from hot water. As predicted, this derivative should exist in the preferred keto configuration in the solid state (31). Its infrared spectrum, Figure 15, therefore exhibits a prominent band near 6.0 μ .

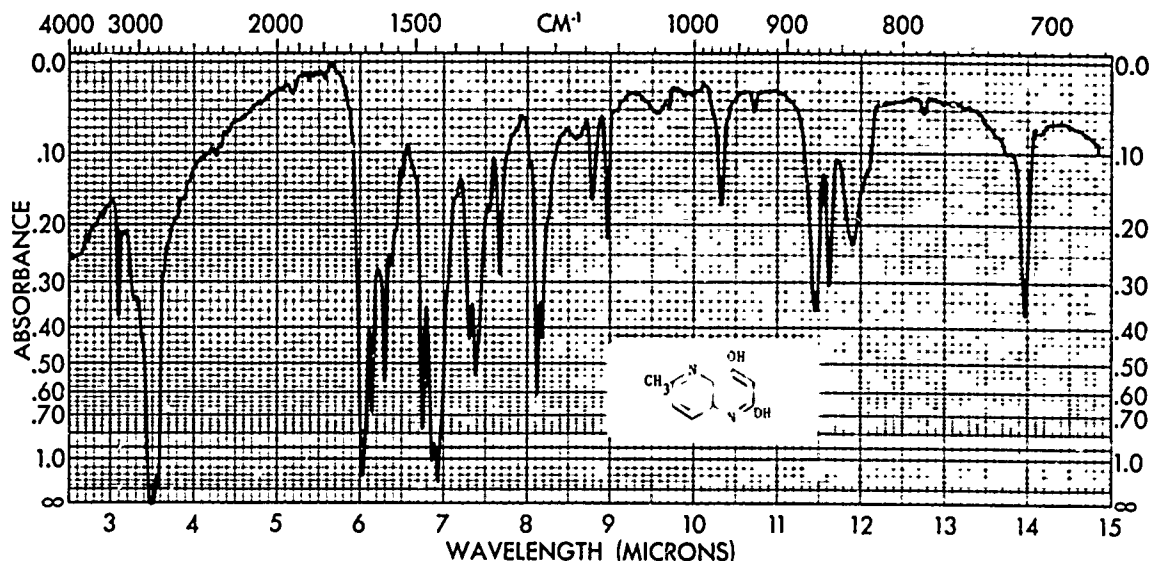
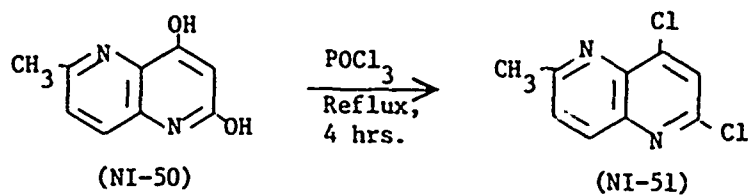


Figure 15. Infrared spectrum of 2,4-dihydroxy-6-methyl-1,5-naphthyridine (nujol mull).

Conversion of NI-50 to the corresponding dichloro derivative, NI-51, was then performed with the use of refluxing phosphorus oxychloride.



The analytically pure dichloro derivative, NI-51, was isolated in 60% yield as a white solid by sublimation. Its proton spectrum, Figure 16, is completely in accord with the formulated structure.

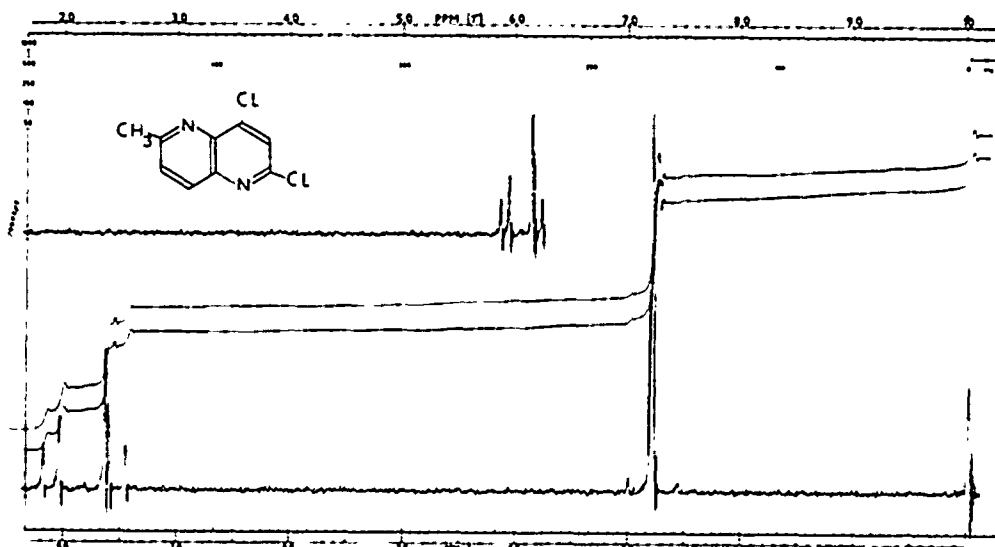
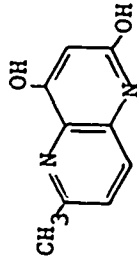
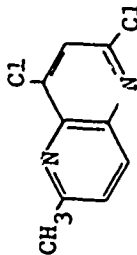


Figure 16. Proton spectrum of 2,4-dichloro-6-methyl-1,5-naphthyridine (CDCl_3).

Table 3

6-Methyl-1,5-Naphthyridine Intermediates

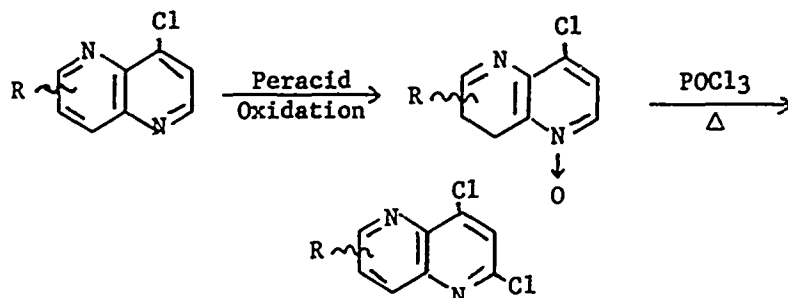
Structure	M.P., °C	Elemental Analysis				Theory Found
		C	H	N	Cl	
 (NI-50)	305-308	61.36	4.58	15.91	0.00	--
		61.77	4.44	15.59	--	
 (NI-51)	134-136	50.73	2.84	13.15	33.28	
		50.39	2.92	12.91	32.70	

3.2.2 EMME-N-OXIDE Synthetic Route to 2,4-Dichloro-1,5-Naphthyridines

The essential features of the EMME-N-OXIDE route to variously substituted 2,4-dichloro-1,5-naphthyridines are depicted in Scheme 7.

Scheme 7

EMME-N-OXIDE Route to 2,4-Dichloro-1,5-Naphthyridines

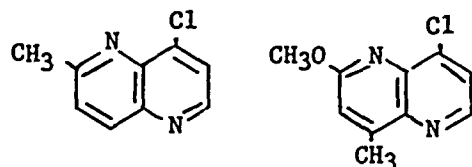


As seen by inspection of Scheme 7, requisite in this procedure is the selective oxidation of the ring-1 nitrogen atom of the performed 4-chloro-1,5-naphthyridines exclusive of oxidation of the ring-5 nitrogen. Once this critical step has been accomplished, subsequent reduction of the ring-1 N-oxide and simultaneous introduction of the 2-chlorine functionality may be accomplished via the conventional Meisenheimer reaction. We originally utilized this route last year as an alternative procedure for the formation of 2,4-dichloro-1,5-naphthyridine (R = H, 12). This year, we have proven the generality of this approach in that it has provided access to a variety of 6-substituted-2,4-dichloro-1,5-naphthyridines which would be otherwise very difficult to obtain via conventional techniques.

The starting materials listed in Scheme 7 are the 4-chloro-1,5-naphthyridines. These materials may be conveniently prepared via the conventional EMME (ethoxymethylenemalonate) procedure. Price and Roberts were the first to apply this procedure as a general route to the formation of quinoline antimalarials (32). Goldberg has since proven the applicability of this approach for the formation of 1,5-naphthyridine antimalarials (5). We utilized this technique last year for the preparation of several 6-substituted-4-chloro-1,5-naphthyridines (12). Our synthesis of additional 4-chloro-1,5-naphthyridines this year via the convention EMME procedure is explained in detail immediately below. The remaining steps in the EMME-N-OXIDE route are fully described in the subsequent section.

EMME Procedure

This year, we have applied the EMME procedure for the formation of the following 4-chloro-1,5-naphthyridines:

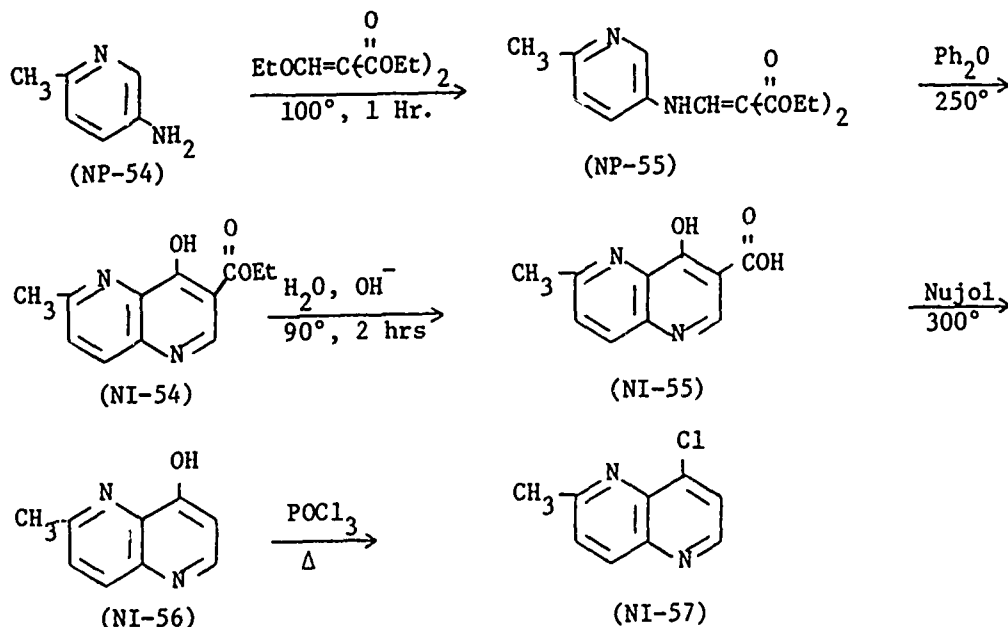


The synthetic progress attained to date is explained in detail below, and the precursors and intermediates characterized this year are included in Table 4 at the end of this section along with their physical constants and full analytical data.

As previously described in Section 3.2.1, the synthetic procedure as outlined in Scheme 6 affords a viable route to the desired 2,4-dichloro-6-methyl-1,5-naphthyridine (NI-51). However, several low yield steps were initially encountered in this synthesis. We, therefore, concurrently explored our recently developed EMME-N-OXIDE procedure as an alternative route to ensure the preparation of the desired target structures. The details of the EMME procedure are applied to the formation of the requisite 4-chloro-6-methyl-1,5-naphthyridine are outlined in Scheme 8.

Scheme 8

EMME Route to 4-Chloro-6-Methyl-1,5-Naphthyridine



The condensation of 5-amino-2-picoline, NP-54, with diethyl ethoxymethylenemalonate was conducted at 100° according to our usual technique. The pure diethyl 6-methyl-3-pyridylaminomethylenemalonate (NP-55) was isolated in practically quantitative yield after recrystallization from hot heptane. The thermal cyclization of NP-55 was then conducted in refluxing diphenyl ether. This cyclization was accompanied by extensive decomposition as evidenced by the production of a black reaction mixture. The product, 3-carbethoxy-4-hydroxy-6-methyl-1,5-naphthyridine (NI-54), separated from the reaction mixture upon cooling, and could be obtained pure only by repetitive trituration with hot ethanol. Its infrared spectrum (Figure 17) is somewhat atypical in that it exhibits two distinct peaks in the carbonyl region. The peak near 5.85 μ may be assigned to the ester absorption, and the peak near 6.0 μ may be assigned to the naphthyridone tautomeric form (31).

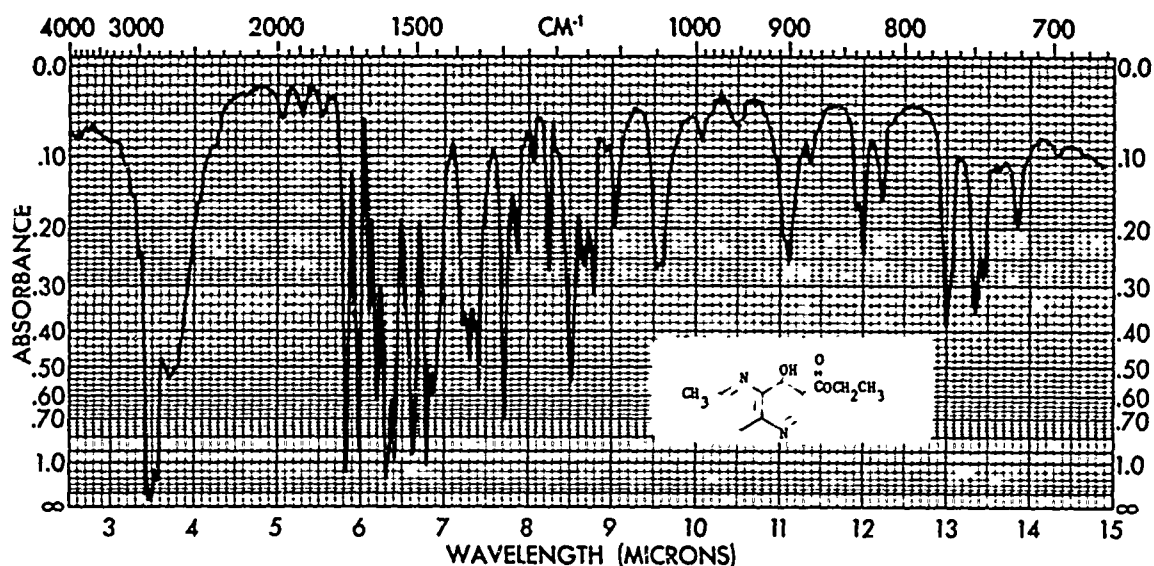


Figure 17. Infrared spectrum of 3-carbethoxy-4-hydroxy-6-methyl-1,5-naphthyridine (nujol mull).

The hydrolysis of the ester group of NI-54 proceeded without any difficulties. The pure acid, NI-55, could be obtained pure in only 57% yield, however, by reprecipitation from aqueous base with hydrochloric acid. The infrared spectrum for the pure acid is reproduced in Figure 18.

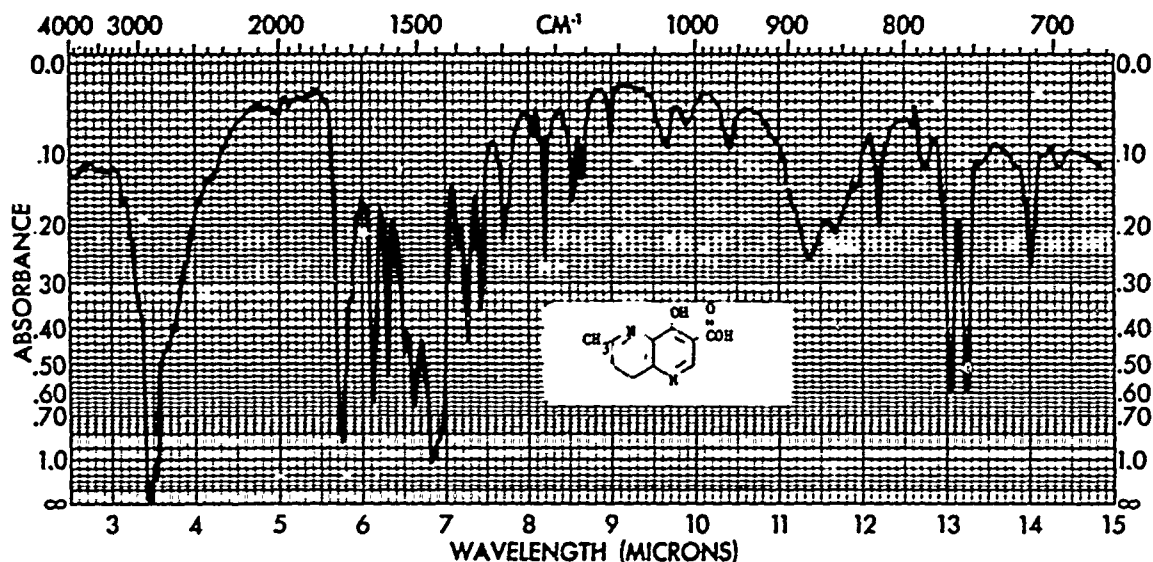


Figure 18. Infrared spectrum of 3-carboxy-4-hydroxy-6-methyl-1,5-naphthyridine (nujol mull).

In the succeeding step, decarboxylation of the acid in refluxing diphenyl ether (250°) was without effect. The decarboxylation proceeded smoothly in nujol at 300°, however, to afford the hydroxy derivative (NI-56) in a crude yield of 93%. The reaction of NI-56 with refluxing phosphorus oxychloride via the standard technique afforded the corresponding pure 4-chloro analog (NI-57) in 63% yield. The infrared and proton spectra for NI-56 and NI-57 are reproduced in Figures 19 and 20 respectively, and are in complete accord with the formulated structures.

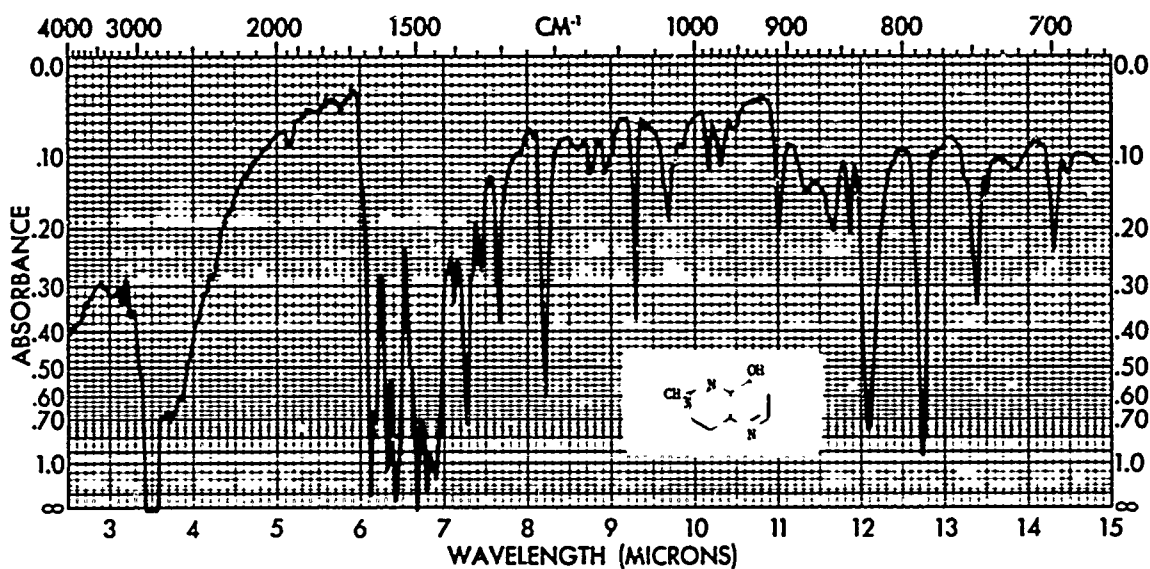


Figure 19. Infrared spectrum of 4-hydroxy-6-methyl-1,5-naphthyridine (nujol mull).

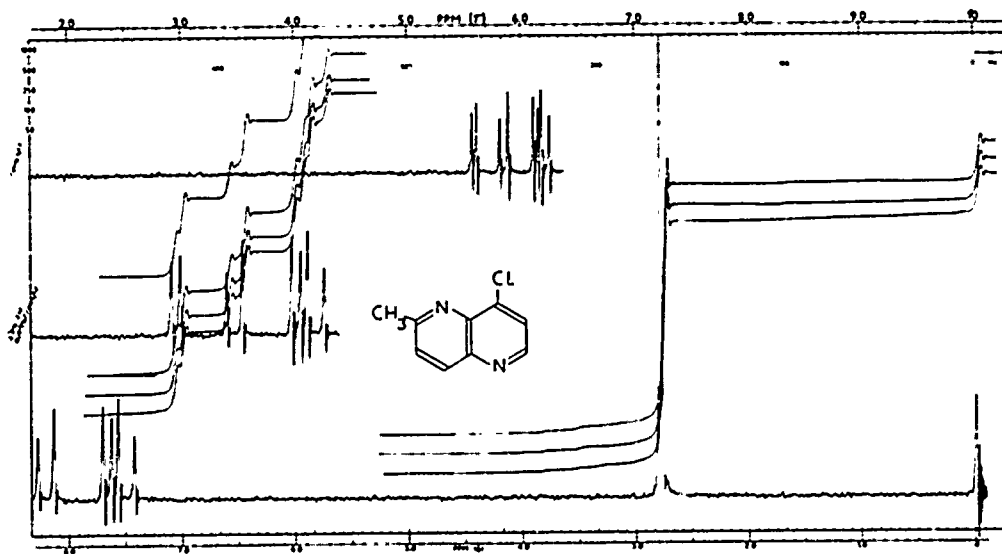
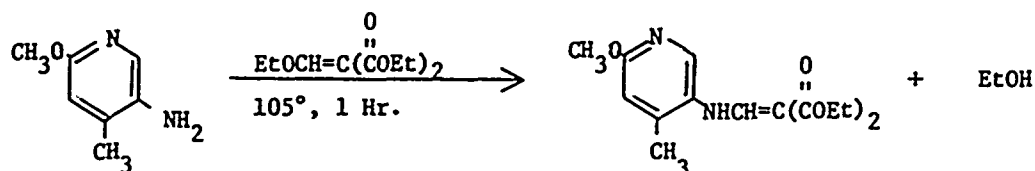


Figure 20. Proton spectrum of 4-chloro-6-methyl-1,5-naphthyridine (CDCl₃).

The application of the *E/AE* technique for the formation of the 4-chloro-6-methoxy-8-methyl-1,5-naphthyridine was also explored this year. Condensation of performed NP-61 with diethyl ethoxymethylenemalonate was conducted via our usual procedure.



The recrystallized acrylate, NP-62, was isolated in 92% yield. The proton spectrum for this precursor is reproduced in Figure 21.

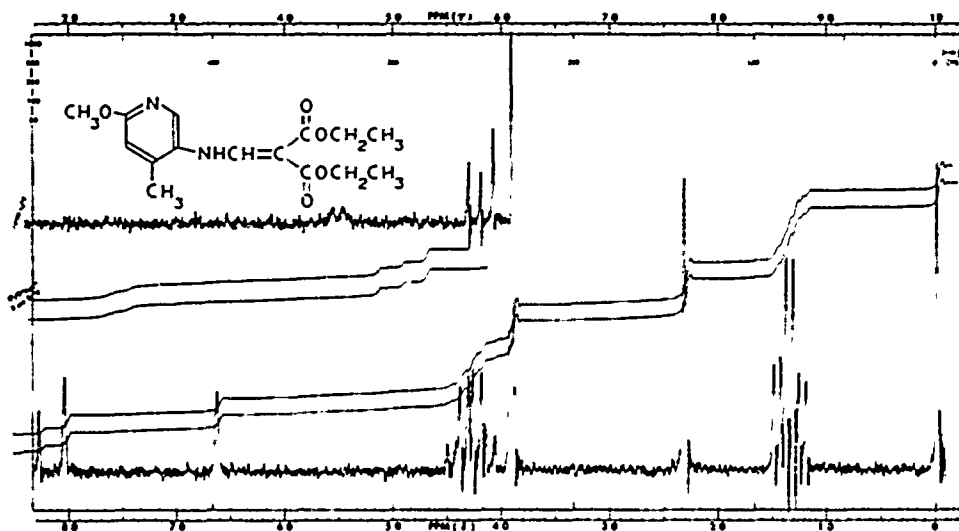
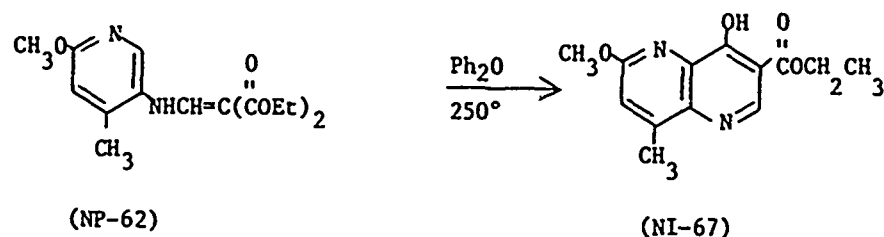


Figure 21. Proton spectrum of diethyl 6-methoxy-4-methyl-3-pyridylamino-methylenemalonate (CDCl_3).

In the succeeding step, the purified acrylate (NP-62) was thermally cyclized in refluxing diphenyl ether.



The crude yield of the resulting ester, NI-67, was only 40%. Part of the problem associated with the low yield at this stage has been attributed to the high solubility of NI-67 in the diphenyl ether. The pure ester was obtained as a white solid after recrystallization from hot ethanol. Its infrared spectrum is reproduced in Figure 22.

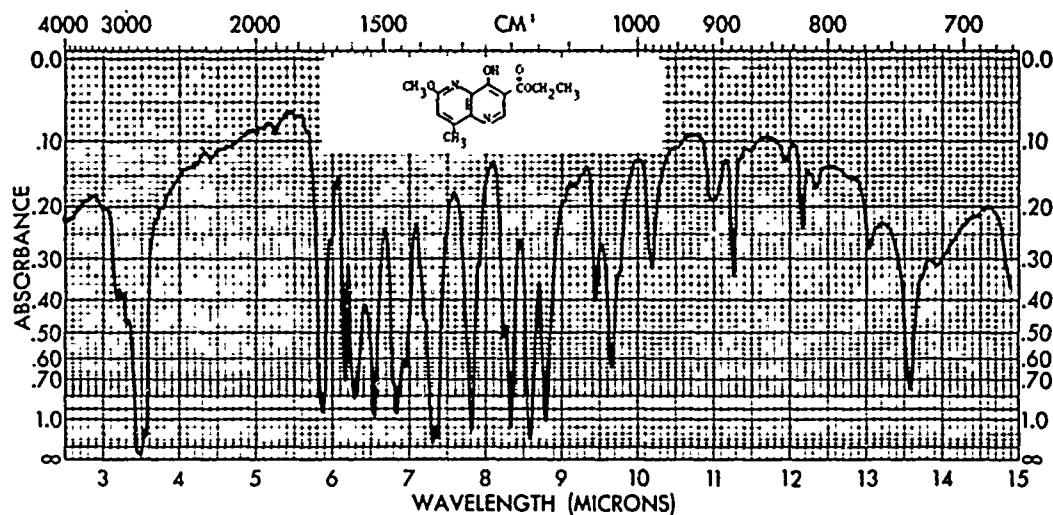
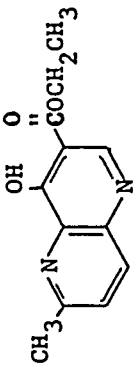
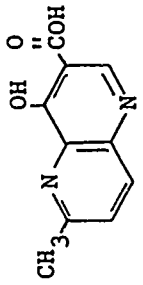
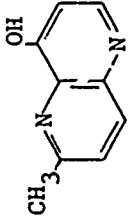
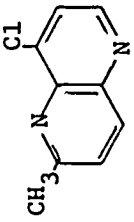


Figure 22. Infrared spectrum of 3-carbethoxy-4-hydroxy-6-methoxy-8-methyl-1,5-naphthyridine (nujol mull).

The succeeding steps in the EMME route to the 4-chloro-6-methoxy-8-methyl-1,5-naphthyridine are presently under investigation and will be reported at a later date.

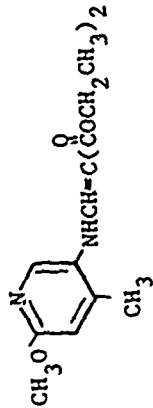
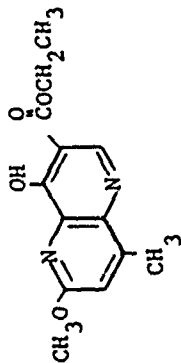
Table 4

Intermediates Prepared Via the EMME Procedure

Structure	M.P., °C	Elemental Analysis			Theory Found
		C	H	N	
 (NP-55)	78-79	60.42 60.39	6.52 6.36	10.07 10.04	
 (NI-54)	291-293	62.06 62.07	5.21 5.02	12.07 11.79	
 (NI-55)	>300	58.82 58.93	3.95 3.99	13.72 13.84	
 (NI-56)	>300	67.48 67.02	5.03 5.11	17.49 17.08	
 (NI-57)	73-75	60.51 60.92	3.95 3.81	15.69(a) 15.86	

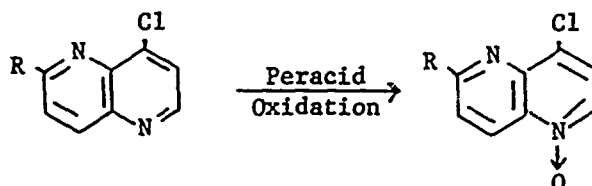
(a) Theory for Cl = 19.85; Found = 19.40.

Table 4 (Cont'd)
Intermediates Prepared Via the EMB Procedure

<u>Structure</u>	<u>M.P., °C</u>	<u>Elemental Analysis</u>		
		<u>C</u>	<u>H</u>	<u>N</u>
 (NP-62)	92-94	58.43 58.43	6.54 6.59	9.09 9.07
 (NI-67)	187-189	59.53 59.12	5.38 5.60	10.68 10.38

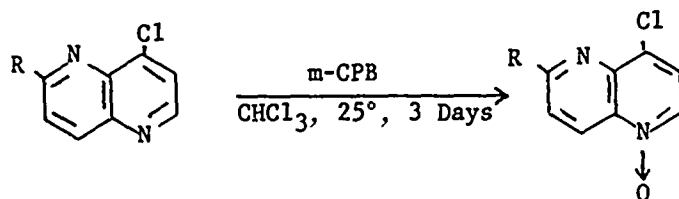
Preparation of 2,4-Dichloro-1,5-Naphthyridines via the EMME-N-OXIDE Route

As previously disclosed in Scheme 7, the critical step in the EMME-N-OXIDE procedure involves the selective oxidation of the ring-1 nitrogen of the performed 6-substituted-4-chloro-1,5-naphthyridines.



A priori, this selective oxidation of the ring-1 nitrogen atom to the complete exclusion of oxidation of the ring-5 nitrogen would seem to be highly speculative. This is particularly true since Hart has reported that 1,5-naphthyridine itself yields a mixture of both its mono- and bis-N-oxides even when reacted with only one mole equivalent of peracetic acid (33). However, we reported last year that the peracetic acid oxidation of 4-chloro-1,5-naphthyridine, NI-38, led to the exclusive isolation of a mono-N-oxide, NI-39, even when the reaction was conducted under forcing conditions with an excess of the peracid (12). Also, as reported last year, unequivocal chemical proof for the selective oxidation of the ring-1 nitrogen atom of NI-39 rested upon its subsequent conversion into 2,4-dichloro-1,5-naphthyridine (NI-15).

This year, we have extended this general procedure for the formation of a variety of 6-substituted-4-chloro-1,5-naphthyridine-1-N-oxides. The most efficient mode of synthesis involved reaction of the appropriately substituted 4-chloro-1,5-naphthyridine with slightly greater than one mole equivalent of m-chloroperoxybenzoic acid (m-CPB) in chloroform solution for three days. A summary of the reactions run to date is included immediately below.



<u>R</u>	<u>NI No.</u>	<u>NI No.</u>	<u>Yield</u>
H	38	39	64
CH ₃	57	66	85
CH ₃ O	28	--	75 (est.)
CF ₃ CH ₂ O	13	43	97
n-BuO	12	44	70
Cl	23	71	74

In the tabulation above, the yield refers to the crude yield of product and in many cases have not been optimized. Also, the 6-methoxy-N-oxide was prepared on a very small scale and was characterized only by spectral means (see below). The analytical data for the newly characterized mono-N-oxides are included in Table 5 at the end of this section. As seen by inspection of Table 5, the analytical data are solely in accord with a mono-N-oxide structure. The proof that only the ring-1 nitrogen atom has been selectively oxidized rests upon chemical transformation (vide infra) and unequivocal spectral evidence. For example, the proton spectrum of 4-chloro-6-methyl-1,5-naphthyridine-1-N-oxide, NI-66, is reproduced in Figure 23.

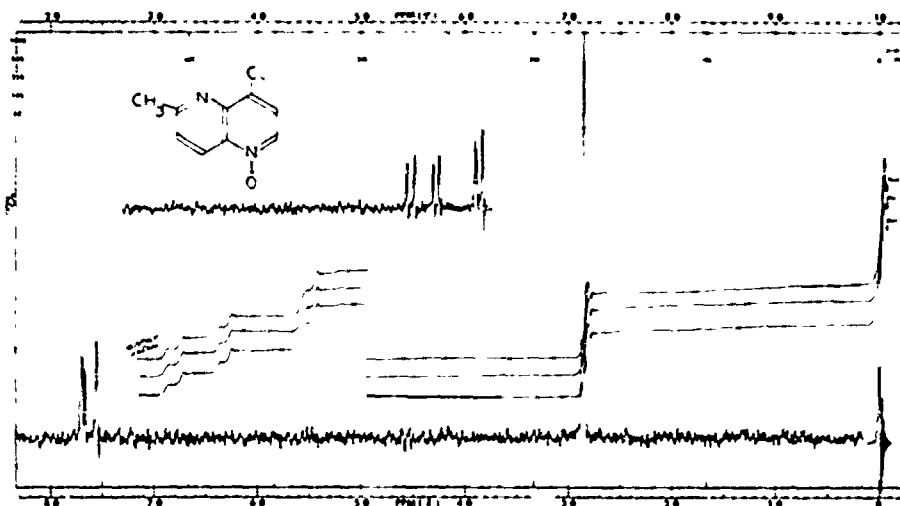


Figure 23. Proton spectrum of 4-chloro-6-methyl-1,5-naphthyridine-1-N-oxide (CDCl_3).

In comparing the proton spectrum of NI-66 with that of its non-oxidized starting material (NI-57, Figure 20), the following significant changes have occurred upon the introduction of the N-oxide grouping. First, there has been an upfield shift of the ring-2 proton resonance ($\Delta\tau = +0.27$ ppm). Secondly, a strong deshielding of the ring-8 proton resonance has occurred ($\Delta\tau = -0.74$ ppm). Finally, there has been an increase of 2.2 Hz in the coupling constant of the ring-2 and ring-3 protons. These findings are only in agreement with the interpretation that the ring-1 nitrogen has been selectively oxidized. Similar spectral shifts are observed in the proton spectra of the remaining 6-substituted-4-chloro-1,5-naphthyridine-1-N-oxides characterized this year (Figures 24-26).

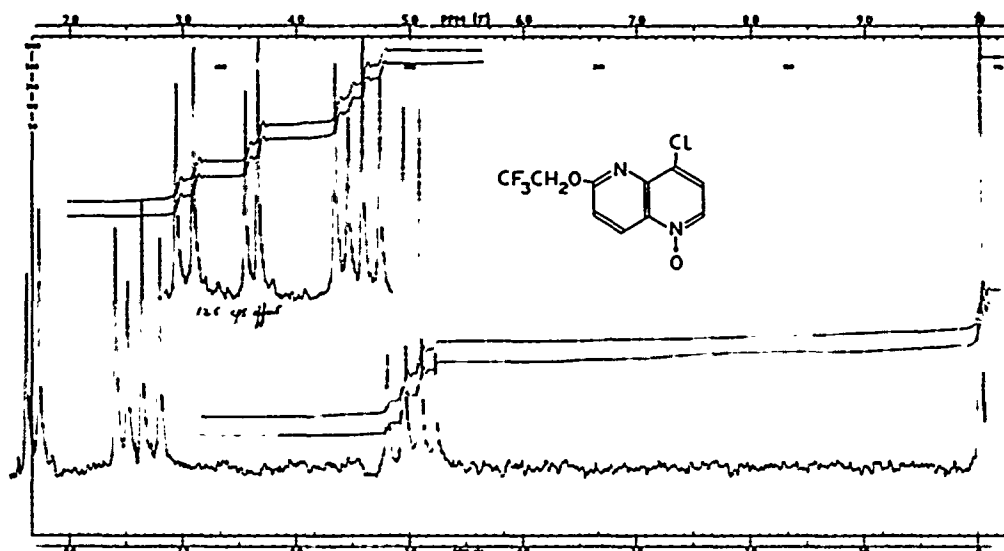


Figure 24. Proton spectrum of 4-chloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine-1-N-oxide (CDCl_3)

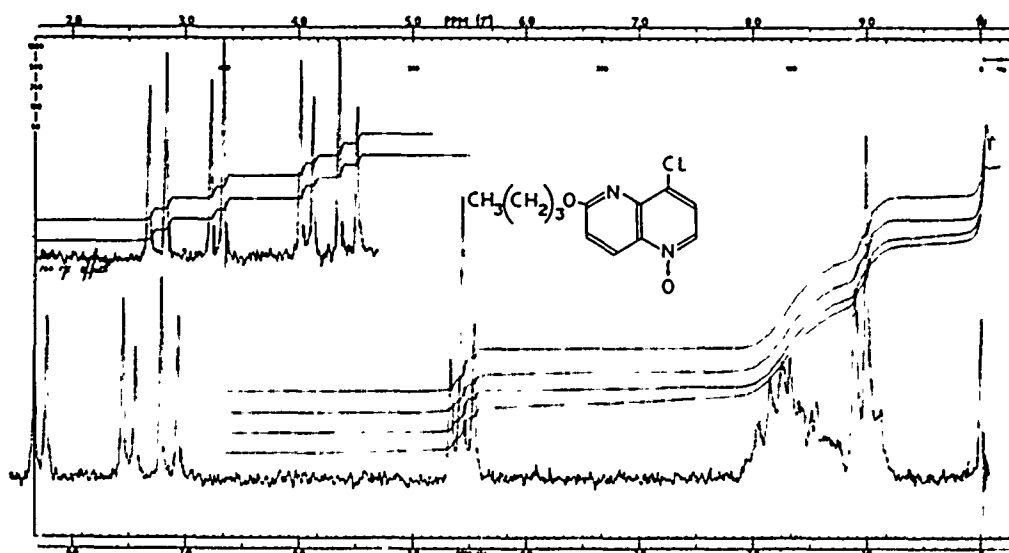


Figure 25. Proton spectrum of 6-n-butoxy-4-chloro-1,5-naphthyridine-1-N-oxide (CDCl_3)

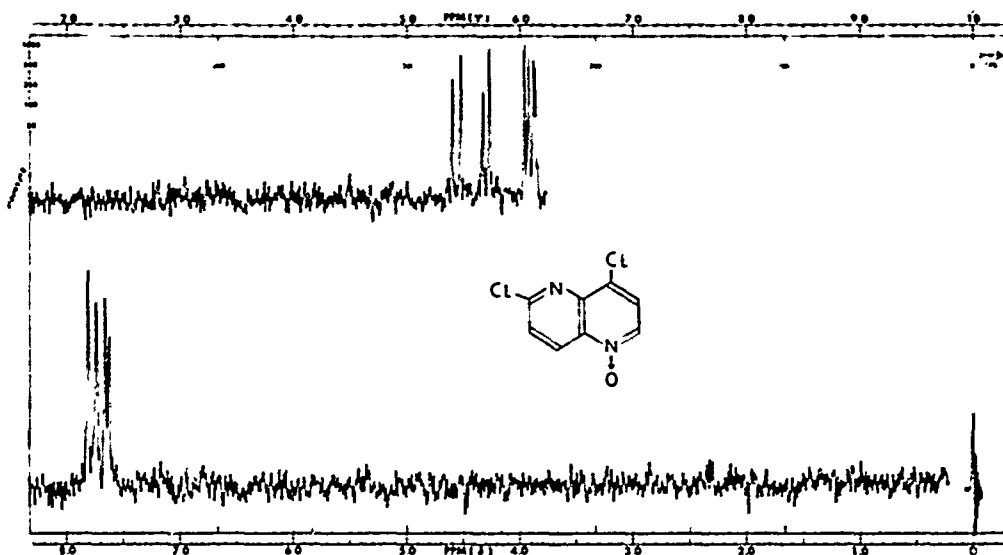
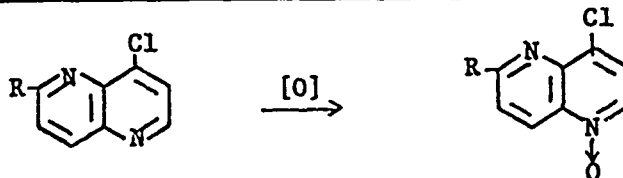


Figure 26. Proton spectrum of 4,6-dichloro-1,5-naphthyridine-1-N-oxide (CDCl_3).

A summary of the changes induced in the proton spectra for each of the compounds characterized to date upon the introduction of the 1-N-oxide grouping is included in the following tabulation.

PROTON SPECTRA OF N-OXIDES



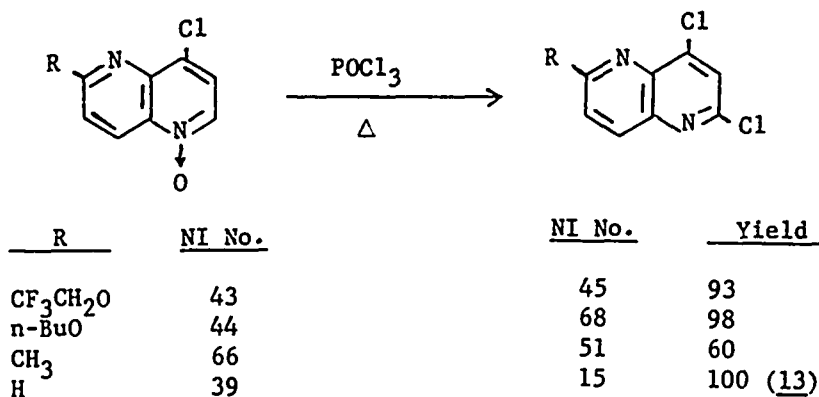
R	$\Delta \tau$ (ppm)				ΔJ (Hz)	
	H-2	H-8	H-3	H-7	2,3	7,8
H	+0.30	-0.71	+0.05	-0.10	+2.1	+0.0
CH_3O	+0.27	-0.71	+0.07	-0.08	+2.3	+0.2
$\text{CF}_3\text{CH}_2\text{O}$	+0.29	-0.69	+0.08	-0.07	+2.2	+0.5
n-BuO	+0.21	-0.71	-0.02	-0.14	+2.1	+0.0
CH_3	+0.27	-0.74	+0.05	-0.15	+2.2	-0.1
Cl	+0.34	-0.65	+0.09	-0.06	+2.1	-0.1
*H (-Cl)	+0.42	-0.68	+0.07	-0.10	+2.9	+0.5

* W. W. Paudler, et. al., J. Het. Chem., 7, 291 (1970)

As shown on the previous page in all cases the significant changes in the proton spectra upon oxidation are: (1) a strong downfield shift of the ring-8 proton resonance; (2) a moderately strong upfield shift of the ring-2 proton resonance; and (3) an increase of about 2 Hz in the 2,3 coupling constant. These correlations are in excellent agreement with the data Paudler has obtained for the mono-N-oxide of the mon-substituted 1,5-naphthyridine (see last entry in the tabulation above, 34).

Our present interpretation for this selective oxidation is based upon steric considerations. While Paudler has demonstrated that the more basic nitrogen atom in the non-substituted 1,x-naphthyridines (x = 6,7) may be selectively oxidized employing m-CPB, he has also reported that he was unable to prepare the bis-N-oxide of 1,8-naphthyridine (34). Since the steric requirements necessary to produce a 5-N-oxide in the presently studied series should be even greater than that required for the preparation of a bis-N-oxide of 1,8-naphthyridine (4-chlorine substituent as compared to a 4-N-oxide grouping), it is easy to understand the selectivity of this reaction. It is of interest to note, however, that it has been reported that the 5-nitrogen atom was selectively oxidized in the benzo-(b)-1,5-naphthyridines (3).

The succeeding step of our general EMME-N-OXIDE synthesis proceeded well in the cases studied to date:



This step involves the general Meisenheimer reaction in which the action of phosphorus oxychloride or surfuryl chloride on the N-oxide function of pyridine or a polycyclic azine results in nucleophilic substitution by the chloride ion at a ring carbon and simultaneous loss of oxygen (36). Based upon full analytical (Table 5) and spectral data (vide infra), the products are formulated as the 2,4-dichloro-1,5-naphthyridines. While the Meisenheimer reaction usually results in a mixture of isomers (37), this is precluded in the presently studied series since the chloride nucleophile can only enter the 2-position. For example, the proton spectrum for the 2,4-dichloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine, NI-45, is reproduced in Figure 27.

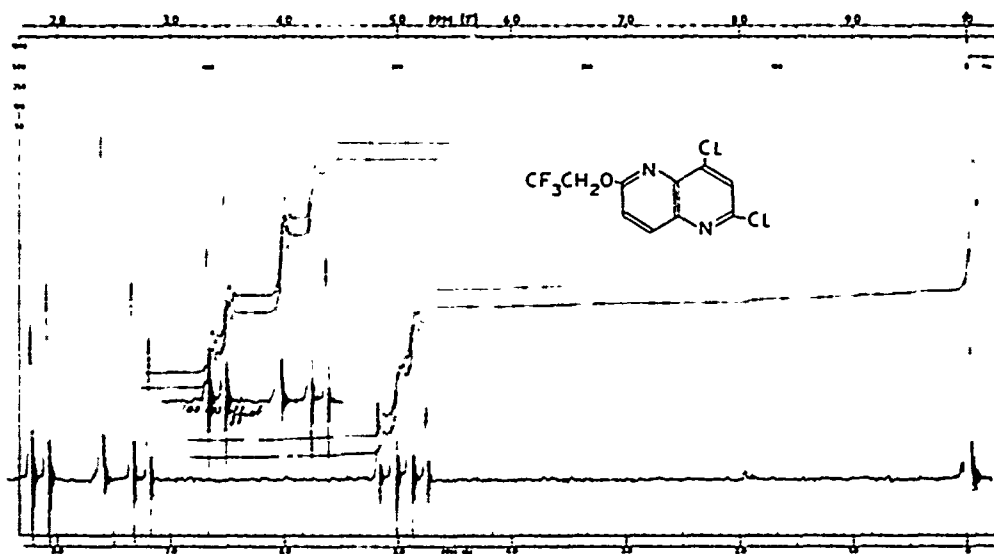


Figure 27. Proton spectrum of 2,4-dichloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (CDCl_3)

As predicted, the ring H-3 resonance of NI-45 is present as a sharp singlet at 2.39 τ . This chemical shift agrees well with that observed for the corresponding proton in the related 2,4-dichloro-1,5-naphthyridine, NI-15, which could also be prepared via an alternative and unambiguous synthetic procedure (2.29 τ , 12, 30). Moreover, the coupling constant for the H-7 and H-8 ring protons (1.83 τ and 2.73 τ , $J_{7,8} = 8.9$ Hz) agrees well with that observed for the A-ring protons of 2,4-dichloro-1,5-naphthyridine (ca., 9 Hz, 12). Since the observed coupling constant is larger than that exhibited by the B-ring protons of 2,4-dichloro-1,5-naphthyridine (ca., 7 Hz, 12), it can be concluded that the structure is as formulated. Also, the possibility of chlorine migration into the A-ring--a distinct possibility in the Meisenheimer reaction (37, 38)--must therefore be discounted. The proton spectrum for the 6-n-butoxy analog (NI-68, Figure 28) also displays the same characteristics.

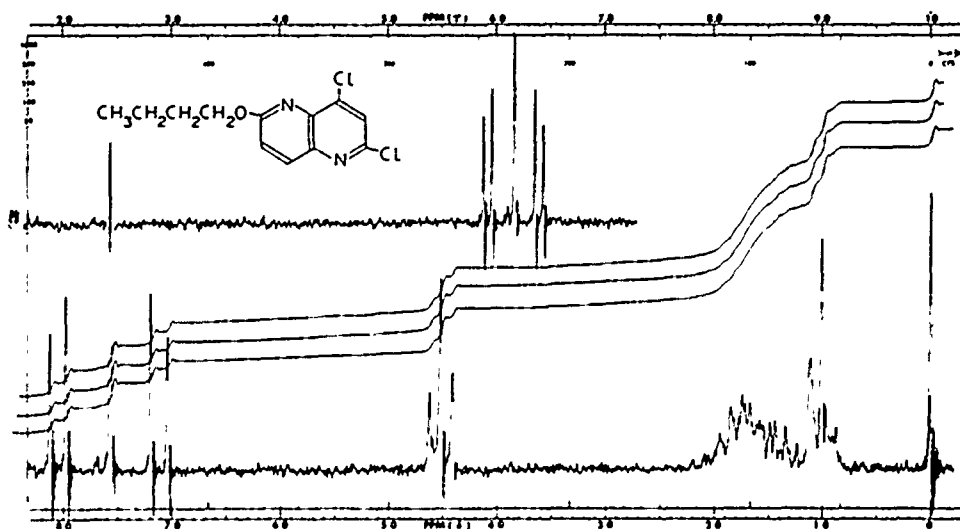


Figure 28. Proton spectrum of 6-n-butoxy-2,4-dichloro-1,5-naphthyridine (CDCl_3).

Table 5
EMME-N-OXIDE Intermediates

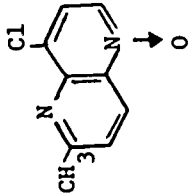
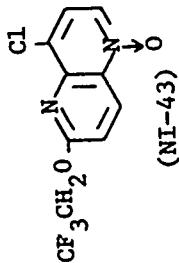
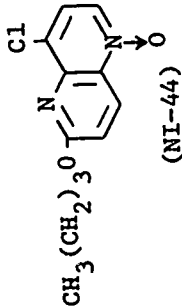
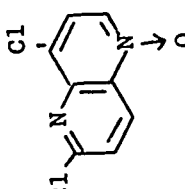
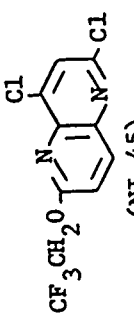
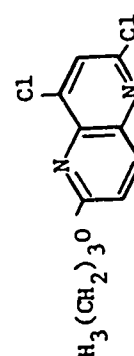
Structure	M.P., °C	Elemental Analysis				Theory Found
		C	H	N	Cl	
 (NI-66)	183-185	55.54	3.63	14.40	18.22	--
		55.14	3.70	14.26	--	
 (NI-43)	178-179	43.10	2.17	10.06	12.73	
		43.23	2.30	10.06	12.93	
 (NI-44)	109-110	57.03	5.18	11.09	14.03	
		57.38	5.20	11.19	13.84	

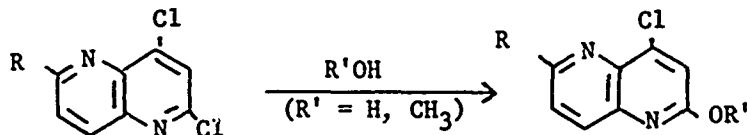
Table 5 (Cont'd)

EMME-N-OXIDE Intermediates

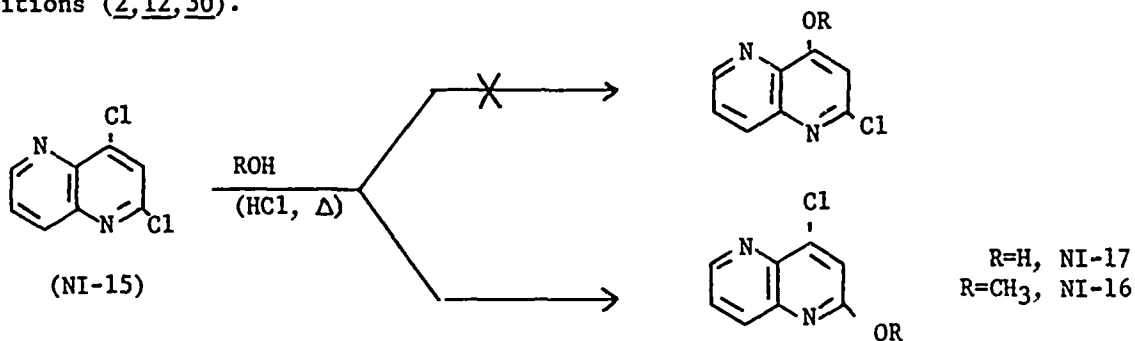
M.P., °C	Structure	Elemental Analysis				Theory Found
		C	H	N	Cl	
203-205		44.68 44.41	1.87 1.98	13.03 12.90	32.98 32.72	
97.0-97.5	 (NI-45)	40.43 40.50	1.70 1.81	9.43 9.44	23.87 24.40	
94-95	 (NI-68)	53.15 52.94	4.46 4.40	16.23 10.41	26.15 --	

3.3 Synthesis of 2-Alkoxy-4-Chloro-1,5-Naphthyridine Intermediates

The succeeding step in our general synthesis of the target structures involves the selective displacement by oxygen nucleophiles at the 2-position in the 6-substituted-2,4-dichloro-1,5-naphthyridines.



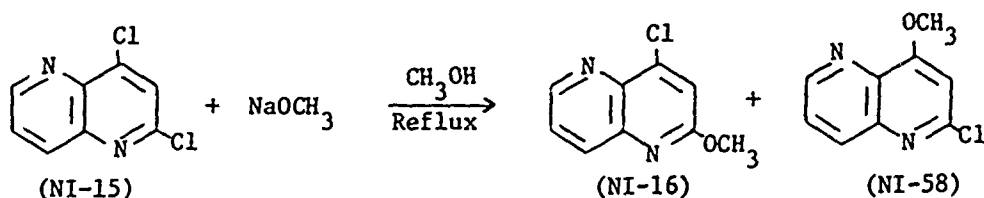
A priori, the reactions depicted above should proceed as indicated. Using an adaptation of the approximate quantum mechanical treatment developed by Longuet-Higgins (39) and subsequently applied to heterocyclic chloro compounds by Chapman (40), Oakes and Rydon have calculated that the 2-chlorine atom present in these 2,4-dichloro-1,5-naphthyridines should be the more reactive (13-15, 30). These 2,4-dichloro-1,5-naphthyridines should, therefore, resemble the 2,4-dichloroquinolines rather than the 2,4-dichloroquinazolines. This has been experimentally verified by the results of our own and other investigations. Indeed, the reaction of 2,4-dichloro-1,5-naphthyridine, itself, with either water or methanol did lead to the exclusive formation of the 2-substituted product, when the reactions were conducted under acidic conditions (2,12,30).



However, we have found that this technique was not generally applicable for the introduction of oxygen functionality into the 2-position of the 6-substituted-2,4-dichloro-1,5-naphthyridines. For example, the reaction of 6-n-butoxy-2,4-dichloro-1,5-naphthyridine, NI-68, with methanolic hydrogen chloride was sluggish (several days at reflux), and a prominent band near 6.0 μ was present in the infrared of the crude product. No reaction at all was observed between NI-68 and methanol itself even after several days at reflux. Also, in the presence of one mole-equivalent of sodium methoxide at room temperature, unreacted starting material was completely recovered. As reported in the experimental section, however, methoxide did react with NI-68 at reflux. In addition to a small quantity of unreacted starting material, two discrete, isomeric products were present in the crude reaction mixture. Substantially the same results were observed for the reaction of 6-(2,2,2-trifluoroethoxy)-2,4-dichloro-1,5-naphthyridine, NI-45, with methanol under either acidic or basic conditions.

In view of the limited quantity of the 6-substituted-2,4-dichloro-1,5-naphthyridines available to us, we therefore restricted our attention this year to the inclusion of methoxy functionality into the 2-position of these intermediates under basic conditions. As a first step toward understanding the mechanism of this reaction, as well as to gain a useful tool for the assignment of absolute structure to each of the isomers produced, we reinvestigated the reaction of 2,4-dichloro-1,5-naphthyridine (NI-15) with methanol under basic conditions.

The reaction of 2,4-dichloro-1,5-naphthyridine (NI-15) with methanol did, indeed, lead to attack at both the 2- and 4-positions under basic conditions.



The crude product mixture was isolated in quantitative yield and exhibited the correct empirical formula (see experimental). However, the proton spectrum of the crude product clearly disclosed the presence of two discrete retroisomers (Figure 29).

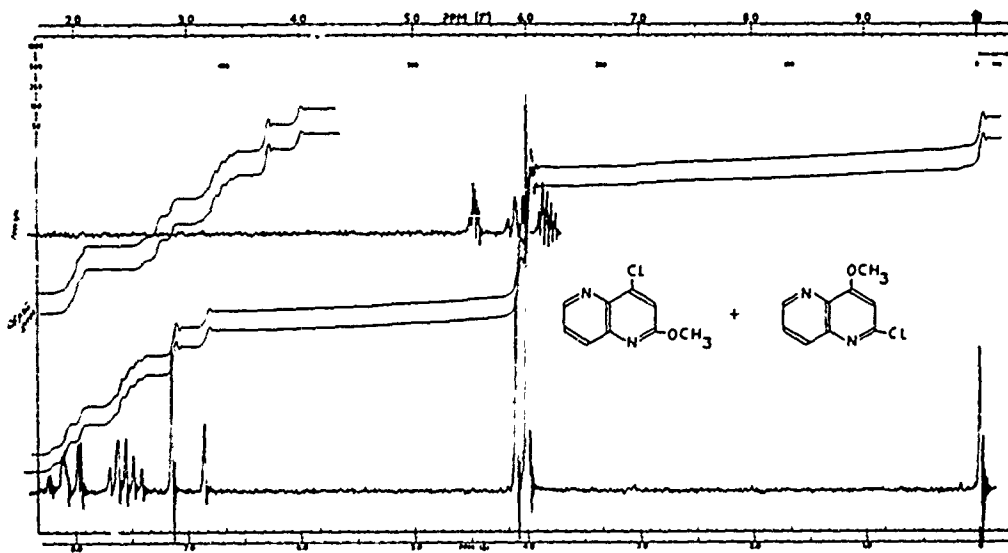


Figure 29. Proton spectrum of 4-chloro-2-methoxy- and 2-chloro-4-methoxy-1,5-naphthyridine reaction mixture (CDCl₃).

Careful fractional crystallization of the crude mixture from heptane led to a clean separation of the two isomers. The less soluble component has been assigned the structure of the 2-chloro-4-methoxy-1,5-naphthyridine (NI-58). The analytical data for NI-58 are included in Table 6, and its proton spectrum is reproduced in Figure 30. The second component present in this mixture had a proton spectrum identical to our previously characterized 4-chloro-2-methoxy-1,5-naphthyridine (NI-16, Figure 31).

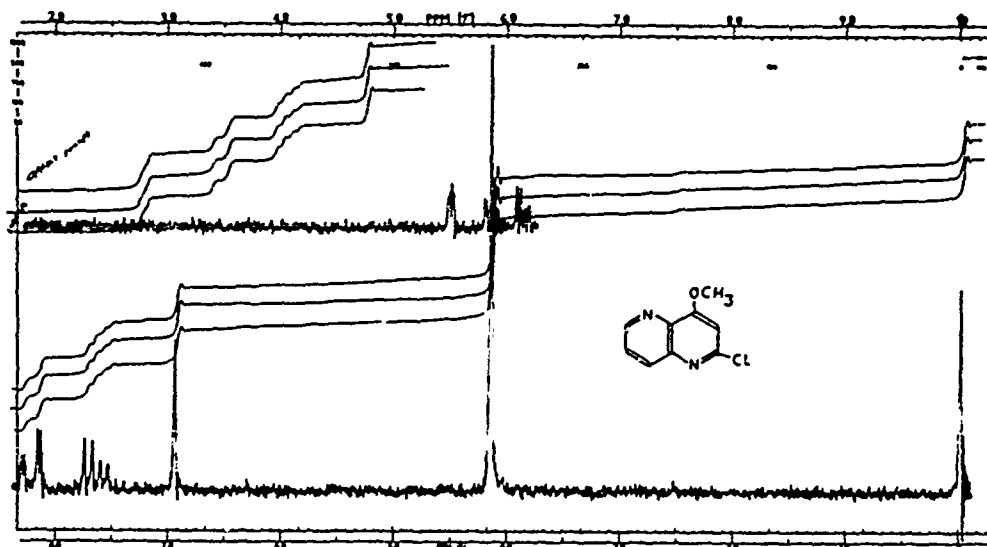


Figure 30. Proton spectrum of 2-chloro-4-methoxy-1,5-naphthyridine (CDCl_3).

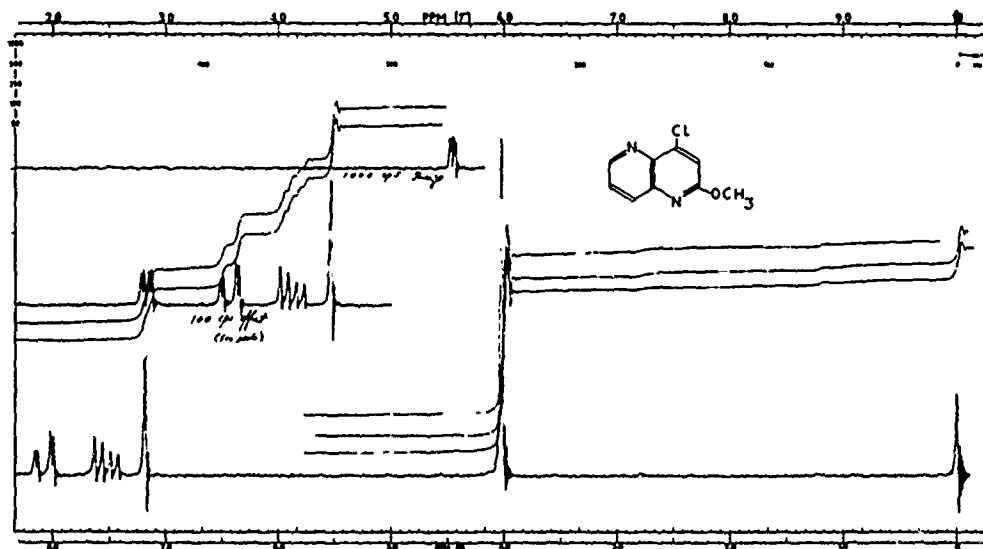
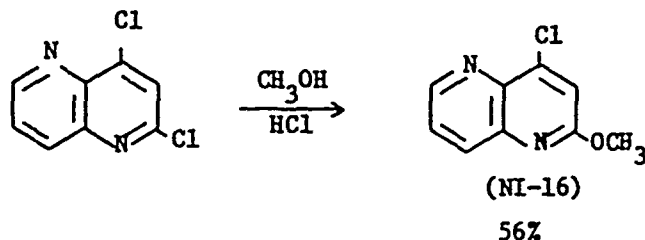
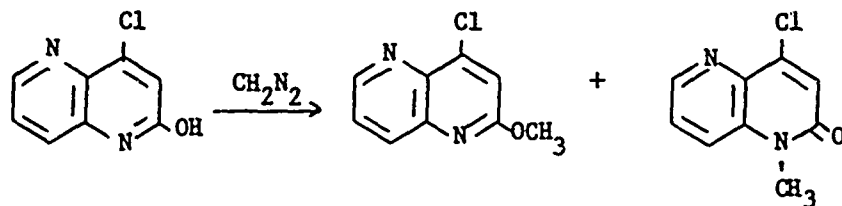


Figure 31. Proton spectrum of 4-chloro-2-methoxy-1,5-naphthyridine (CDCl_3).

The unambiguous assignment of structure to NI-16 and NI-58 is based upon the following argument. As stated earlier, we employed the procedure as reported by Cheng (2) in an initial preparation of NI-16 (12).

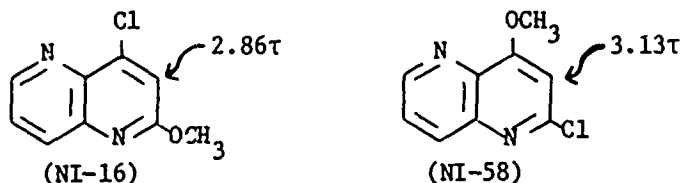


While only a 56% recovery of product could be obtained via this procedure, only one component was present in the isolated product. Moreover, Cheng reported that this product (m.pt. 114-115°) exhibited a proton spectrum identical to the product arising from the O-alkylation of 4-chloro-2-hydroxy-1,5-naphthyridine (2).



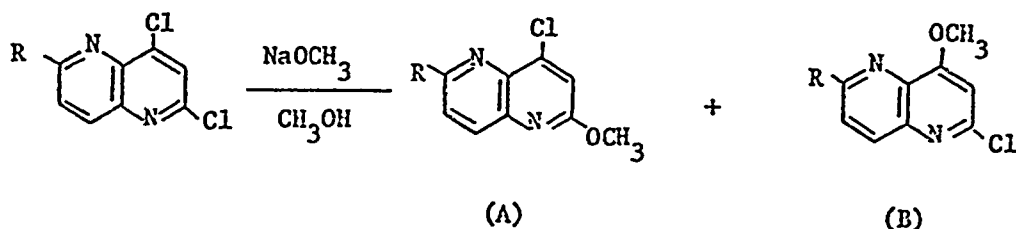
There can be no doubt, therefore, that the product arising from reaction of 2,4-dichloro-1,5-naphthyridine with methanol under acidic conditions must have the 4-chloro-2-methoxy-1,5-naphthyridine structure (NI-16). The structural assignments applied to NI-58 and NI-16 in Figures 30 and 31 are therefore substantiated.

Of utmost importance in the proton spectra of NI-58 and NI-16 is the rather dramatic chemical shift difference exhibited by the respective ring H-3 protons.



This chemical shift of the H-3 protons serves as a useful diagnostic tool for the identification of the respective retrosomers. (vide infra).

In view of the results of this model reaction, it is now clear that the preferential reactivity of the 2-position of the 6-substituted-2,4-dichloro-1,5-naphthyridines is almost totally destroyed when the reactions are conducted under basic, rather than acidic conditions. A mixture of the two possible retroisomers is produced. A summary of the pertinent data gathered to date is included in the following tabulation.



R	A			B		
	NI-No.	% Yield	H-3(τ)	NI-No.	% Yield	H-3(τ)
H	16	60	2.86	58	40	3.13
CH ₃ O	--	35	2.90	42	45	3.12
CF ₃ CH ₂ O	59	20	2.89	46	65	3.17
CH ₃	52	50	2.85	53	50	3.07
CH ₃ (CH ₂) ₃ O	72	30	2.98	69	48	3.09

The respective retroisomers were conveniently separated via their differing solubilities in heptane (see experimental). The analytical data for each of the newly characterized 2- and 4-methoxy derivatives are included in Table 6 at the end of this reaction. The yield of each isomer is not the isolated yield, but an estimation of the percentage of each isomer produced in the crude reaction mixture. This was obtained by a combination of either proton nmr or infrared spectral means. As stated earlier, the chemical shift of the H-3 proton singlet serves as a useful diagnostic tool for the absolute assignment of structure to each of the retroisomers produced. For example, the proton spectra for the 6-(2,2,2-trifluoroethoxy) and 6-methyl retroisomers are reproduced in Figures 32,33 and 34,35 respectively. In each instance, the chemical shifts of the ring H-3 singlet follow the same pattern.

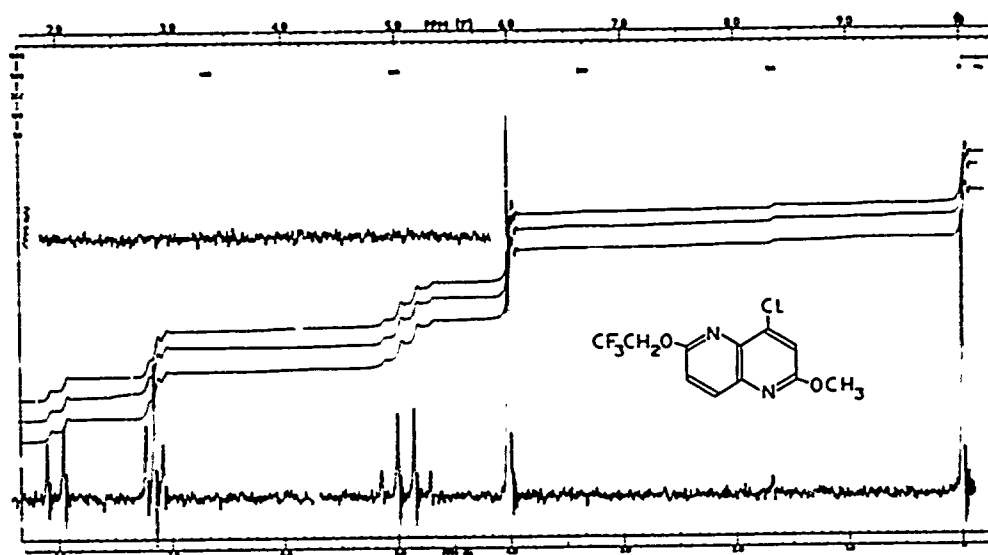


Figure 32. Proton spectrum of 4-chloro-2-methoxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (CDCl_3).

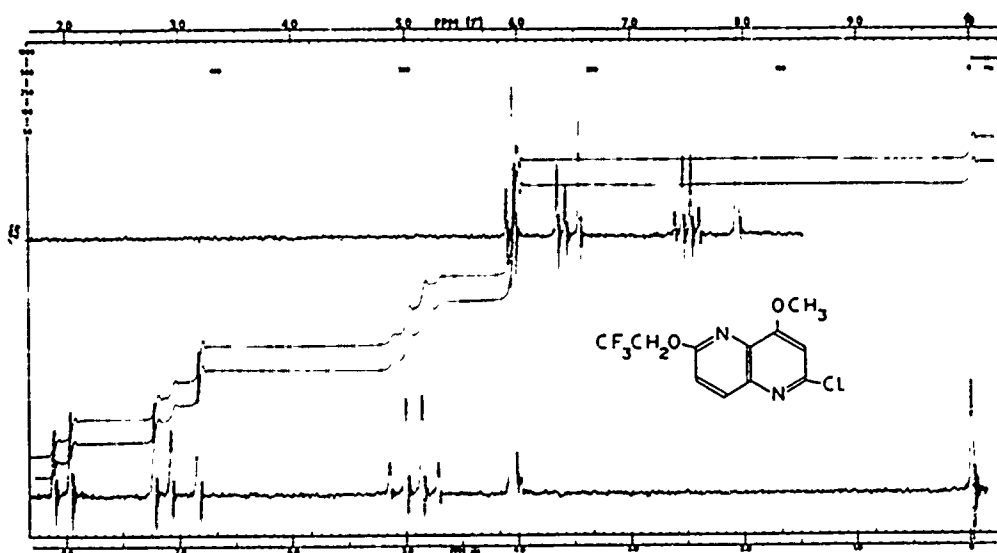


Figure 33. Proton spectrum of 2-chloro-4-methoxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (CDCl_3).

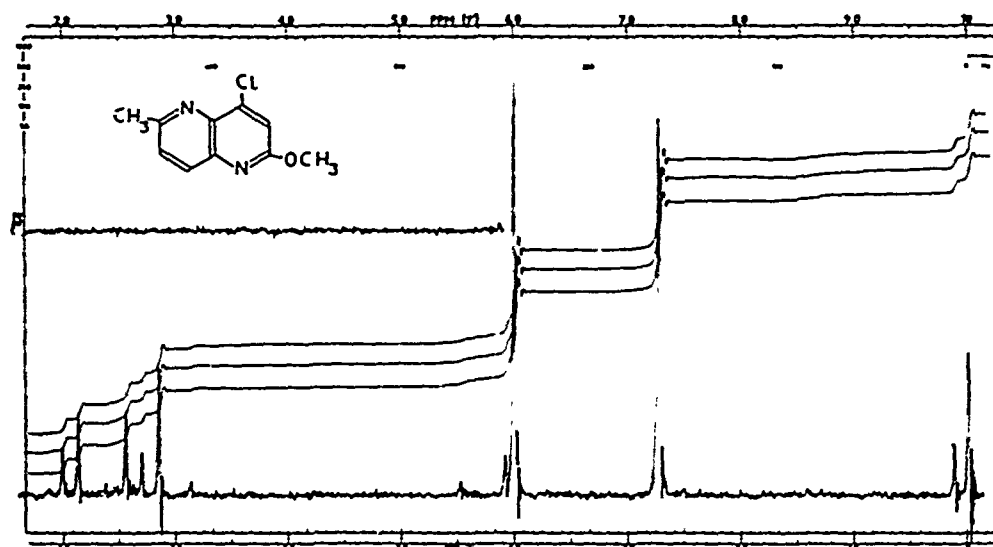


Figure 34. Proton spectrum of 4-chloro-2-methoxy-6-methyl-1,5-naphthyridine (CDCl_3).

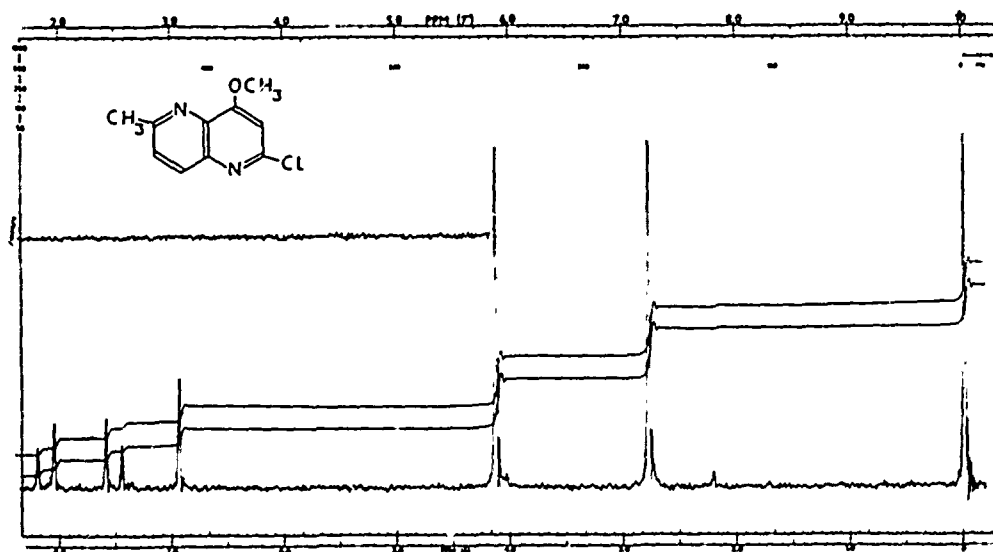


Figure 35. Proton spectrum of 2-chloro-4-methoxy-6-methyl-1,5-naphthyridine (CDCl_3).

It should be noted in the proton spectrum of the 4-chloro-2-methoxy-6-methyl-1,5-naphthyridine, NI-52, that this isomer could not be completely separated from its retroisomer even after exhaustive fractional recrystallization from heptane as attested by the minor resonances present in Figure 34. Substantially the same results were obtained with the two 6-n-butoxy retroisomers (Figures 36 and 37). The darkened peaks in Figure 36 represent the presence of either unreacted starting material or its retroisomer. In all instances, however, satisfactory analytical data were obtained (Table 6).

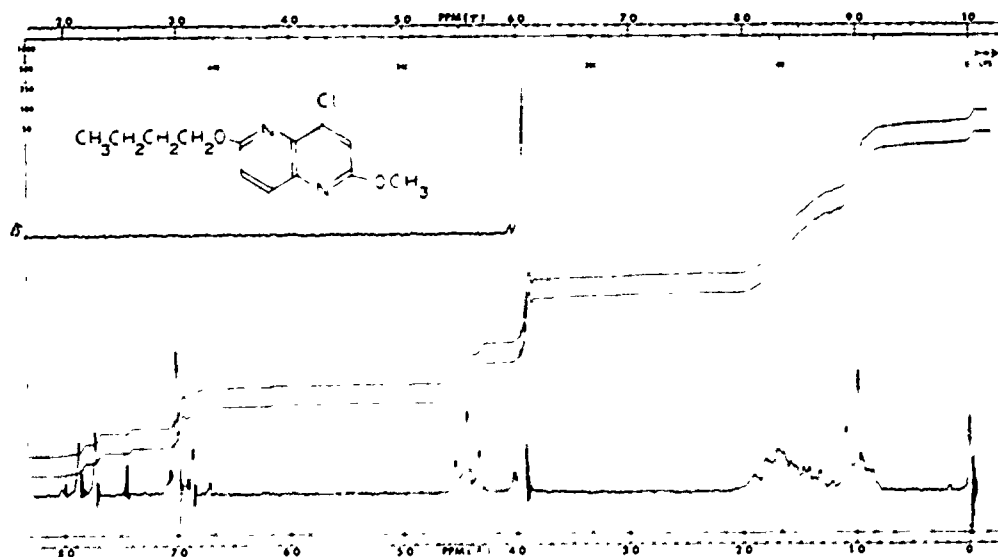


Figure 36. Proton spectrum of 6-n-butoxy-4-chloro-2-methoxy-1,5-naphthyridine (CDCl_3).

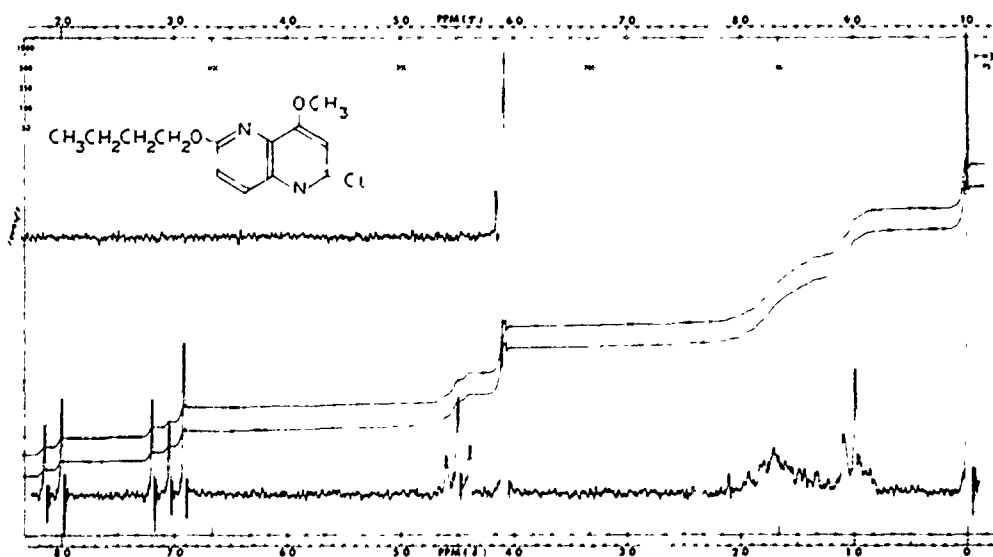


Figure 37. Proton spectrum of 6-n-butoxy-2-chloro-4-methoxy-1,5-naphthyridine (CDCl_3).

In the reactions of 6-methoxy-2,4-dichloro-1,5-naphthyridine (NI-57) with methoxide, virtually identical results were obtained. In this instance, however, we have not as yet been able to cleanly separate and characterize the desired 2-methoxy-4-chloro intermediate. However, it is now clear from the chemical shift of the H-3 proton of the isomer characterized to date (NI-42, 3.12 τ , Figure 38) that this must be the 4-methoxy-2-chloro isomer.

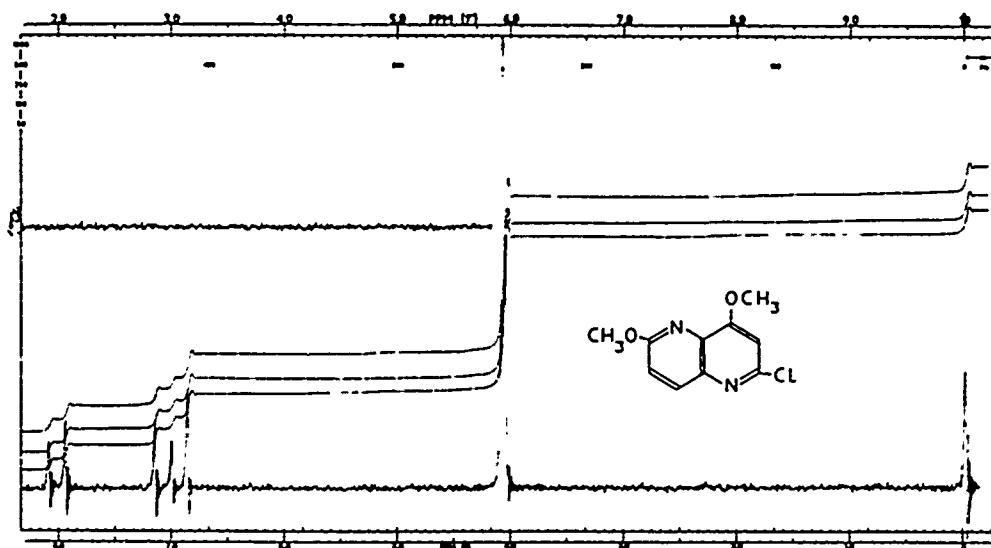
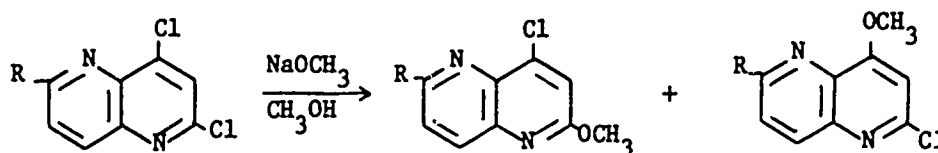


Figure 38. Proton spectrum of 2-chloro-4,6-dimethoxy-1,5-naphthyridine (CDCl_3).

In summary, it is now clear that in the reactions of methoxide with the 6-substituted-2,4-dichloro-1,5-naphthyridines, a mixture of the two possible retroisomers is produced (in addition to a small amount of by-product).



These retroisomers may be separated based upon their differing solubilities in heptane; the 2-methoxy-4-chloro isomers being the more soluble in all cases. Also, the chemical shift of the H-3 proton in these retroisomers serves as a useful diagnostic tool for their structural assignment.

Table 6

2,4-(Chloro, Methoxy)-1,5-Naphthyridine Intermediates

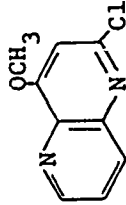
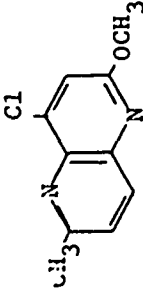
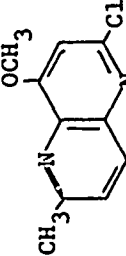
Structure	M.P., °C	Elemental Analysis				Theory Found
		C	H	N	Cl	
 (NI-58)	103-104	55.54	3.63	14.40	18.22	--
		55.63	3.65	14.43	--	
 (NI-52)	86-89	57.56	4.35	13.43	16.99	16.90
		57.37	4.38	13.16	16.90	
 (NI-53)	144.5-145.0	57.56	4.35	13.43	16.99	16.90
		57.64	4.46	13.27	16.90	

Table 6 (Cont'd)

2,4-(Chloro, Methoxy)-1,5-Naphthyridine Intermediates

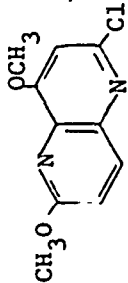
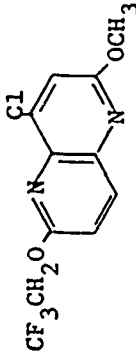
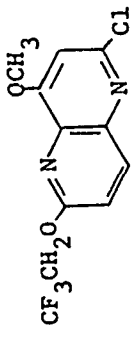
Structure	M.P., °C	Elemental Analysis				Theory Found
		C	H	N	Cl	
 (NI-42)	156.0-157.5	53.46 53.30	4.04 3.99	12.47 12.40	15.78 16.23	
 (NI-59)	107-108.5	45.14 45.14	2.75 2.68	9.57 9.49	12.12 --	
 (NI-46)	113-115	45.14 45.49	2.75 2.78	9.57 9.69	12.12 12.32	

Table 6 (Cont'd)

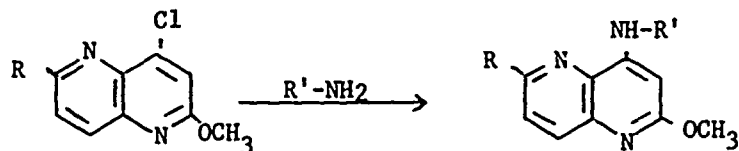
2,4-(Chloro, Methoxy)-1,5-Naphthyridine Intermediates

Structure	M.P., °C	Elemental Analysis			
		C	H	N	Cl
<chem>COc1nc2cc(COC)ccc2n1</chem> CH ₃ (CH ₂) ₃ O Cl (a) 105-110° (0.02 mm) (NI-72)		58.53 58.49	5.67 5.47	10.51 10.58	13.29 --
<chem>COc1nc2cc(COC)ccc2n1</chem> CH ₃ (CH ₂) ₃ O OCH ₃ Cl (NI-69)	103-105	58.53 58.64	5.67 5.78	10.51 10.46	13.29 --

(a) Molecular distillation.

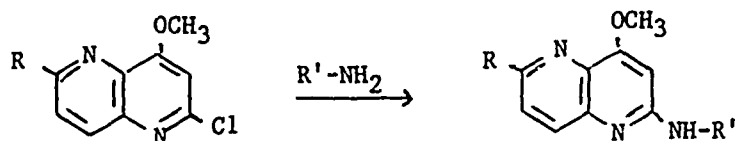
3.4 Synthesis of Target Structures

As previously illustrated in Scheme 1 of this report, the final step in our overall synthesis of the target 4-amino-1,5-naphthyridines involves the reaction of diamines with our previously characterized 6-substituted-4-chloro-2-methoxy-1,5-naphthyridine intermediates.



R = Alkyl, Alkoxy
R' = Pamaquine, Pentaquine and Primaquine Side Chains

A full discussion of the results obtained to date in the utilization of this procedure for the isolation of the desired target structures is presented below. In addition, at the specific request of Walter Reed personnel, we have also explored the reactions of diamines with the 6-substituted-2-chloro-4-methoxy-1,5-naphthyridine retroisomers as a general route to the 2-amino-1,5-naphthyridine target structures.

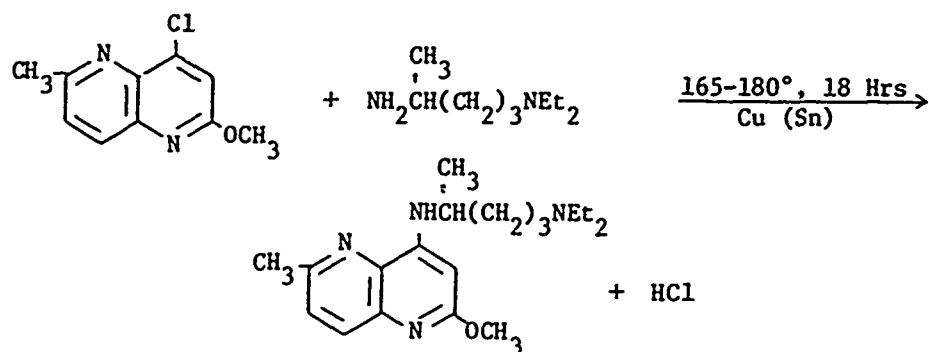


The results acquired to date in each of these two general areas will be discussed in turn. Also, all of the compounds which were characterized and submitted for biologic testing in conjunction with these studies are included in Table 7 at the end of this section along with their physical constants and full analytical data.

4-Amino-1,5-Naphthyridines

The general synthetic techniques which are applicable for inclusion of the diamine side chains have been discussed in full detail in our last annual report (12). Our synthetic efforts for last year were directed at the inclusion of alkoxy substituents into either the 6- or the 2-position of the 4-amino-1,5-naphthyridines. This year, our efforts in the title area were extended to the inclusion of substituents (alkyl and alkoxy) into the 6-position of the 2-methoxy-4-amino-1,5-naphthyridines.

The inclusion of the 6-methyl group has been effected this year by the reaction of 4-chloro-2-methoxy-6-methyl-1,5-naphthyridine, NI-52, with the diamine corresponding to the pamaquine side chain.



The analytically pure product, 2-methoxy-6-methyl-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine, was isolated as a viscous, amber oil in 51% yield by molecular distillation. The analytical data are included in Table 7 at the end of this section, and its proton spectrum is reproduced in Figure 39. As predicted, the methoxy resonance is present as a sharp singlet at 5.99 τ , and the 6-methyl resonance is present as the singlet at 7.40 τ (overlapping the N-CH₂ quartet). Of utmost importance, however, is the appearance of the 4-amino resonance as the broad doublet near 3.55 τ . The lowfield shift of this doublet conclusively proves that the diamine side chain has been introduced into the 4-, rather than the 2-position. The structural assignments ascribed to NI-52 and NI-53 in the preceeding section are therefore substantiated. If the 2-amino-4-methoxy retroisomer of the depicted compound were produced, its 2-amino resonance would appear at a higher field strength (τ = 3.69 and 4.77 for the 4- and 2-amino protons respectively present in our previously characterized 2,4-di-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine, NI-32, (12).

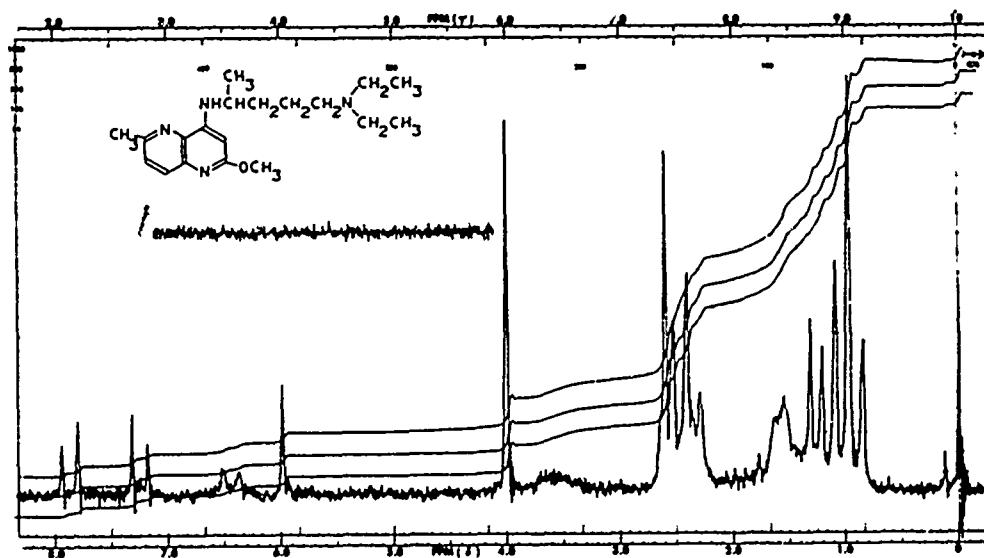
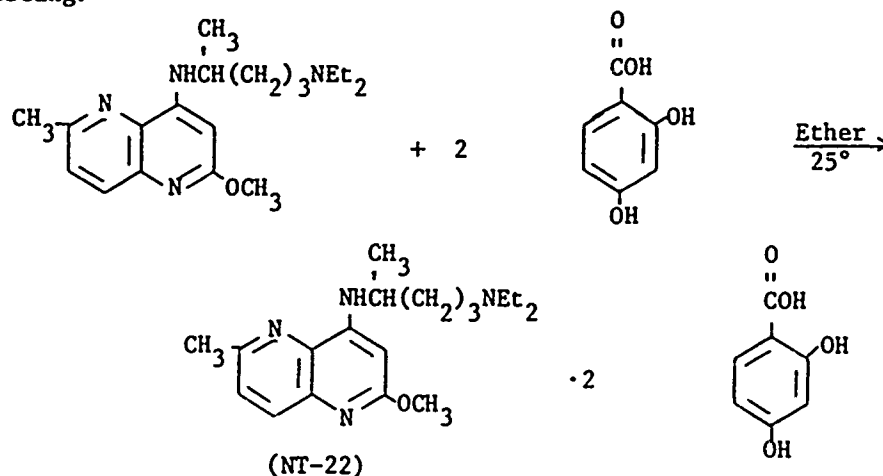


Figure 39. Proton spectrum of 2-methoxy-6-methyl-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (CDCl₃)

The free base prepared as described above was not submitted to WRAIR, but was converted to its di- β -resorcylate salt for biologic testing.



The salt immediately separated from the reaction mixture and was isolated by filtration under a nitrogen atmosphere. The analytical data are included in Table 7, and its infrared spectrum is reproduced in Figure 40.

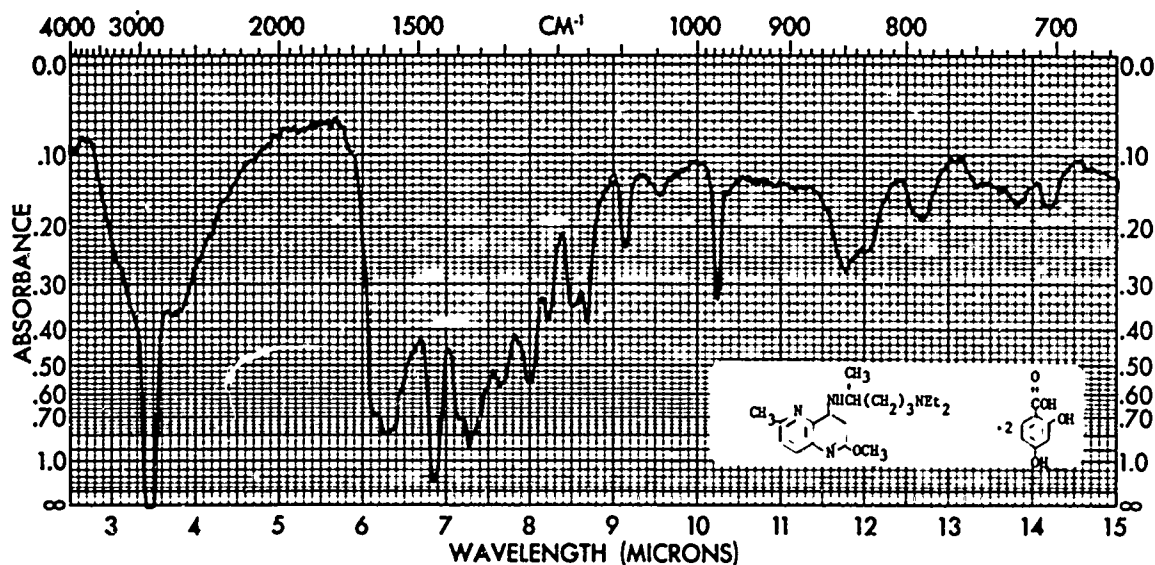
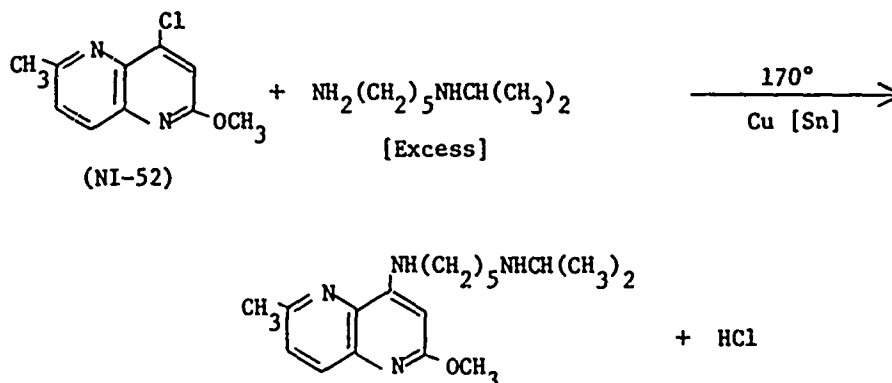
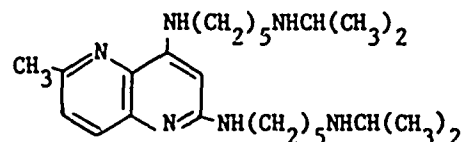


Figure 40. Infrared spectrum of 2-methoxy-6-methyl-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine di- β -resorcylate (nujol mull).

This year, we have also attempted to extend this procedure for the inclusion of the corresponding pentaquine side chain. Accordingly, our performed 4-chloro-2-methoxy-6-methyl-1,5-naphthyridine, NI-52, was reacted with 5-isopropylaminopentylamine (41) in accord with our standard technique.



However, upon work-up of the reaction mixture, only a very low yield (ca., 0.2g; CH₃O, 6.01τ) of the desired product could be identified in an early cut of the molecular distillation. The sole product isolated in analytically pure form to date has proven to be 2,4-di-(5-isopropylamino-pentylamino)-6-methyl-1,5-naphthyridine.



This product, NI-63, was isolated in 31% yield as an amber oil which slowly formed a low melting solid after standing. Its proton spectrum (Figure 41) clearly discloses the loss of the 2-methoxy group in this reaction. Moreover, the presence of two broad triplets at 3.57τ and 5.00τ (the 4-amino and 2-amino protons respectively) conclusively proves that the diamine side chain has been introduced into both the 2- and 4- positions (12).

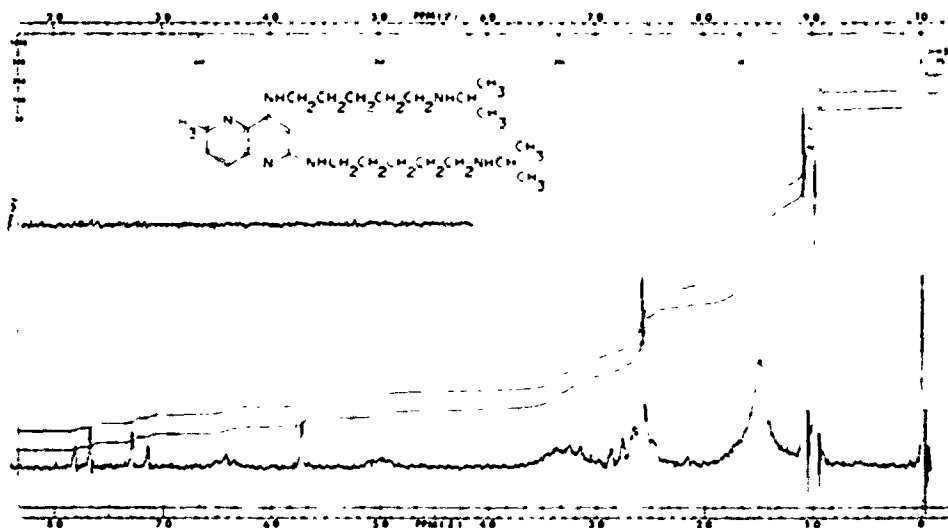
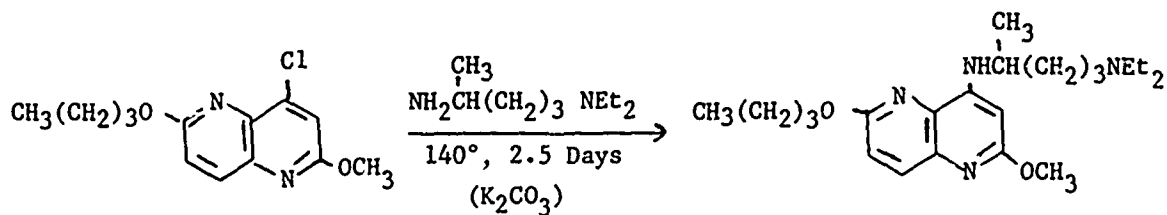


Figure 41. Proton spectrum of 2,4-di-(5-isopropylaminopentylamino)-6-methyl-1,5-naphthyridine (CDCl_3).

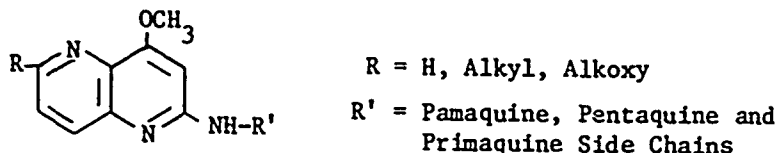
To date, our efforts directed at the formation of 4-amino-1,5-naphthyridines which incorporate both the 6-alkoxy and the 2-methoxy groups have not been particularly rewarding. Displacement reactions of diamines on the 4-position of NI-59 and NI-72 were conducted under a variety of conditions. In general, reactions run at 170° for eighteen hours led to as yet uncharacterizable derivatives. Proton spectral measurements taken on the crude reaction mixtures disclosed that the 2-methoxy groups were also lost under these conditions. However, we have very recently found that this competitive displacement of the 2-methoxy group may be circumvented if the reactions are conducted under less forcing conditions. For example, the reaction of NI-72 with novaldiamine has afforded the desired target structure when the reaction was conducted at lower temperature (140°) for an extended period of time.



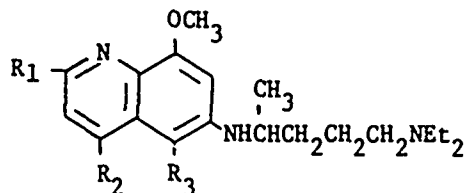
The free base was separated from the crude reaction mixture by column chromatography, and the depicted target structure has very recently been characterized as its di- β -resorcylate. We are presently utilizing this technique for the inclusion of a variety of 6-alkoxy substituents. The results of these investigations will be reported at a later date.

2-Amino-1,5-Naphthyridines

At the most recent Contractor's Antimalarial Conference at WRAIR (42), it was requested that we should explore the possibility of preparing 2-amino-1,5-naphthyridine analogs of the following type.

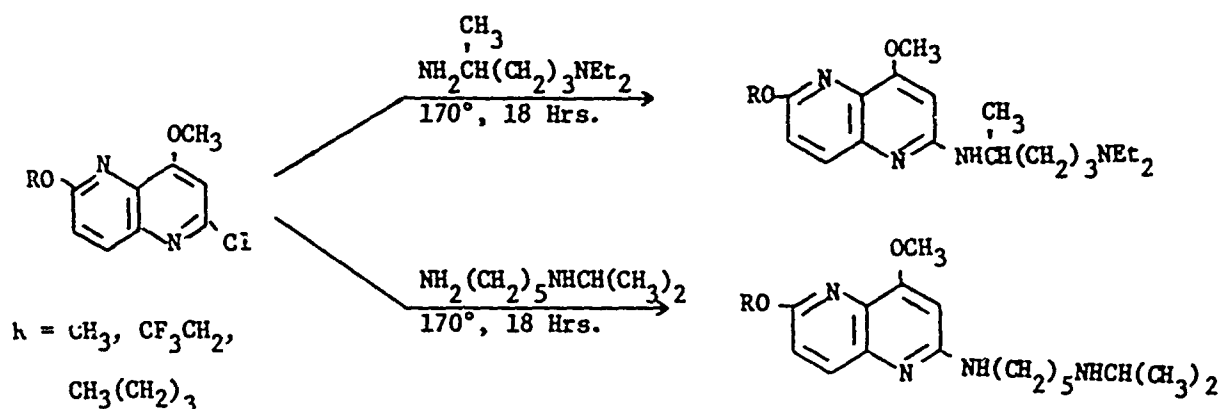


The rationale for the synthesis of these derivatives undoubtedly rested upon the similarity of these structures to certain 6-aminoquinolines,

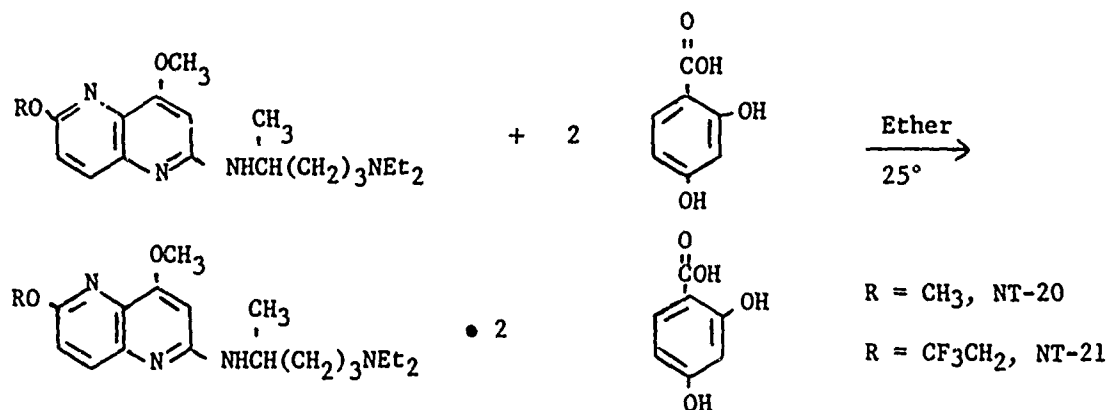


which have been reported to exhibit prophylactic activity against malaria (43). Accordingly, we have applied a limited synthetic effort this year to develop a useful preparative route to these analogs. A priori, the most direct route to the 2-amino-1,5-naphthyridines would involve the reaction of our previously characterized 6-substituted-2-chloro-4-methoxy-1,5-naphthyridines with diamines. The synthetic progress attained this year utilizing this approach is explained below.

As depicted by the equations below, the reactions of the 6-alkoxy-2-chloro-4-methoxy-1,5-naphthyridine intermediates (NI-42, NI-46, and NI-69) with the diamines corresponding to the pentaquine and pamaquine side chains were conducted this year in accord with our standard technique.



The reactions directed at the inclusion of the pamaquine side chain were not particularly facile, and considerable amounts of unreacted starting material were present even when conducted in the presence of copper-bronze catalyst at 170° for eighteen hours. Also, the isolation of products from each of these reactions via molecular distillation afforded only low yields of distillable material. The pamaquine side chain products derived from the 6-methoxy- and 6-(2,2,2-trifluoroethoxy)- intermediates, NI-42 and NI-46, could only be isolated in yields of 30% and 19% respectively. To date, we have been unable to isolate a characterizable derivative from the reaction of the 6-n-butoxy analog, NI-69. Indeed, in the latter reaction, the only isolable material proved to be a thick gum which distilled over a fairly broad range. Moreover, examination of the proton spectrum of this gum disclosed the loss of the 4-methoxy group. While we presently can offer no interpretation of this result, part of the problem may lie in the atmospheric oxidation of the products produced in these reactions. For example, the free bases derived from the reactions of NI-42 and NI-46 were observed to rapidly darken and become very viscous upon standing at room temperature overnight. For characterization purposes, the free bases were therefore immediately converted into their di-β-resorcyate salts in ether solution at 25°.



Both products, NT-20 and NT-21, were isolated by filtration under a nitrogen atmosphere. Each of these derivatives proved to be extremely hygroscopic, and the 4,6-dimethoxy analog, NT-20, consistently analyzed as a hemi-hydrate (Table 7). The infrared spectra for both NT-20 and NT-21 are included in Figures 42 and 43 respectively.

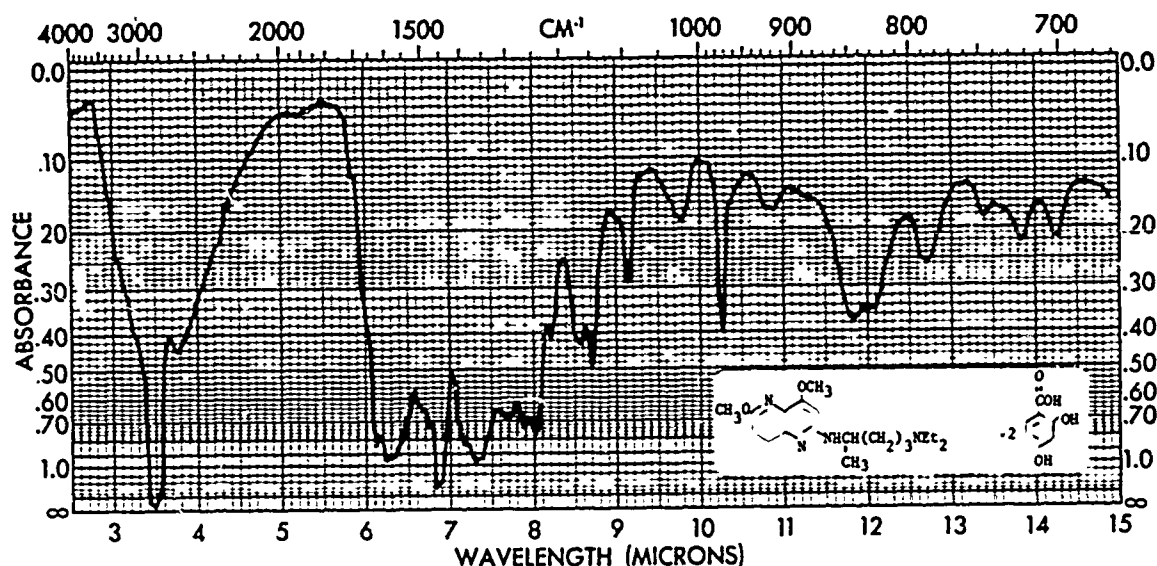


Figure 42. Infrared spectrum of 4,6-dimethoxy-2-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine di- β -resorcyate hemi-hydrate (nujol mull).

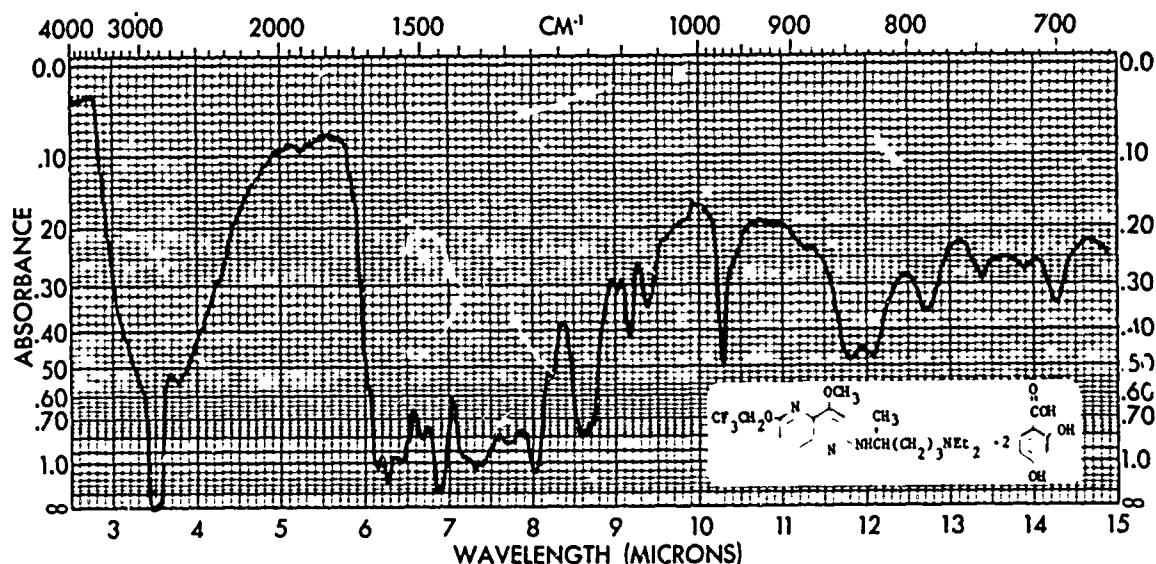
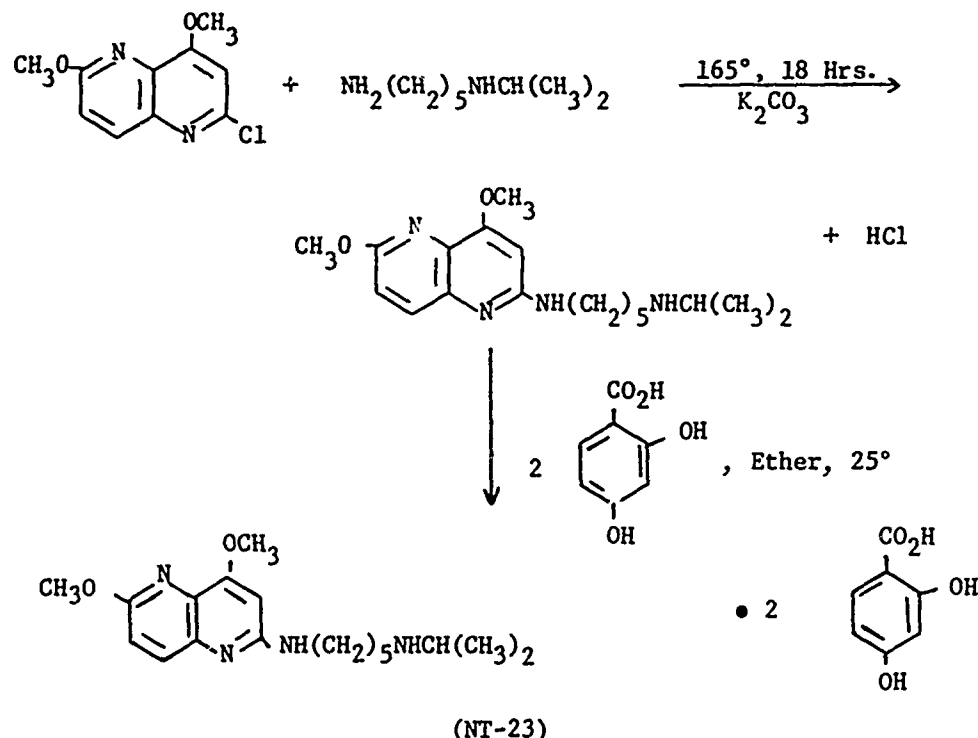


Figure 43. Infrared spectrum of 4-methoxy-6-(2,2,2-trifluoroethoxy)-2-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine di- β -resorcyate (nujol mull).

The reactions of NI-42, NI-46 and NI-69 with 5-isopropylamino-pentylamine (41) as a route to the pentaquine side chain analogs were also not particularly rewarding in that extensive tar formation accompanied the condensations. To date, only the 4,6-dimethoxy-2-(5-isopropylaminopentyl-amino)-1,5-naphthyridine could be isolated in high enough yield for characterization as its di- β -resorcyate salt, NT-23.



In this instance, the initial displacement reaction was conducted in the presence of one mole-equivalent of potassium carbonate which served as an acid scavenger for the hydrochloric acid produced in the reaction. The free base was isolated by molecular distillation i.e. 43% yield as a yellow oil. A sample of this free base quickly darkened and became very viscous upon exposure to air. The di- β -resorcyate salt was therefore immediately prepared by the dropwise addition of a slight excess of 2,4-dihydroxybenzoic acid in ether into an ether solution of the free base at room temperature. The salt immediately separated from solution and was isolated as an extremely hygroscopic white solid. This material, NT-23, consistently analyzed as a hemi-hydrate (Table 7). Proton spectral measurements confirm its formation in that two methoxy singlets of equal intensity were present at 5.98 and 6.01 (dilute solution in deuteromethanol). The infrared spectrum for this derivative is reproduced in Figure 44.

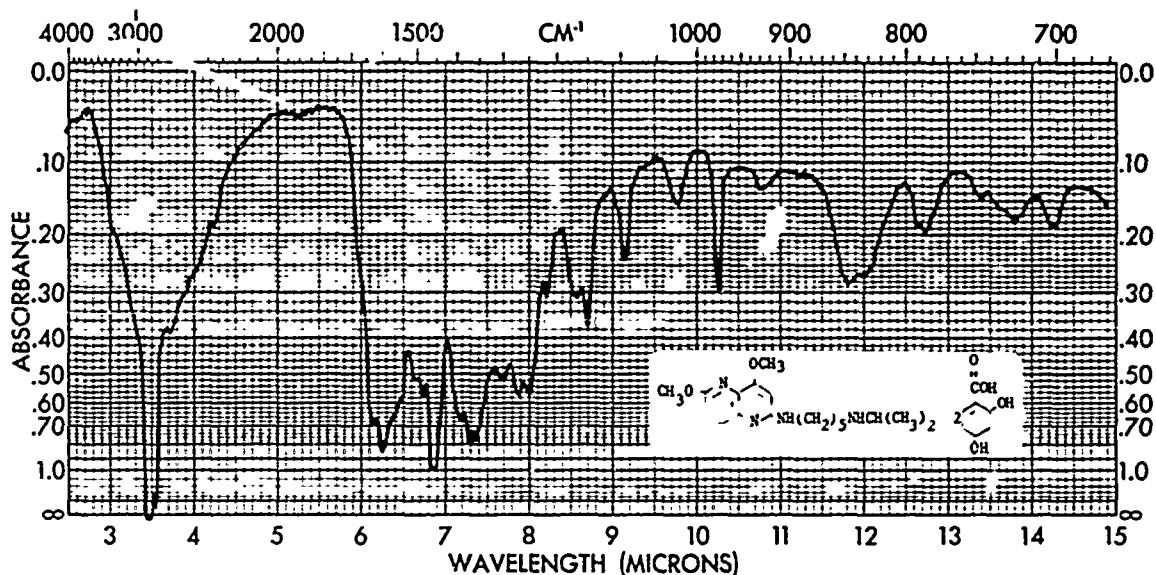
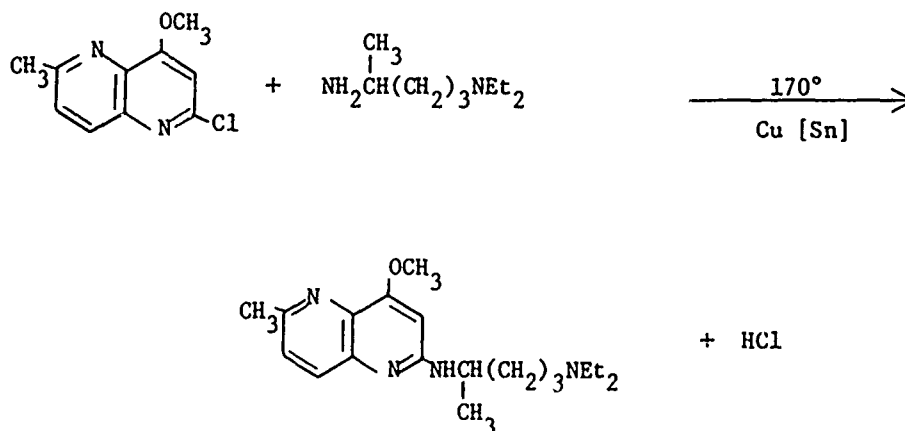
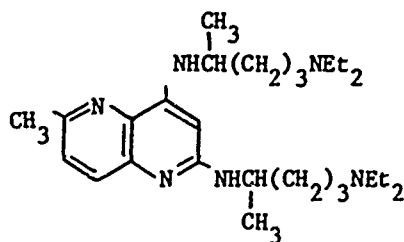


Figure 44. Infrared spectrum of 4,6-dimethoxy-2-(5-isopropylaminopentyl-amino)-1,5-naphthyridine di-β-resorcylate hemi-hydrate (nujol mull).

The extension of this reaction to include the 6-alkyl, rather than the 6-alkoxy functionality, was also explored this year. For example, we attempted the reaction of 2-chloro-4-methoxy-6-methyl-1,5-naphthyridine, NI-53, with novaldiamine as a route to the corresponding pamaquine side chain derivative.



In this instance, however, the desired product was not obtained, and the sole isolable derivative proved to be the corresponding 2,4-diamino-analog,



This product, NI-64, was isolated in 66% yield. The structural assignment for NI-64 again rests upon full analytical data (Table 7 and its proton spectrum (Figure 45). That the 4-methoxy group has been lost in this reaction is readily apparent by the conspicuous absence of a methoxy singlet near 6.0 τ . The 4-amino doublet is present near 3.64 τ , and the 2-amino proton resonance is present as the singlet at 2.50 τ (aged sample in CDCl_3).

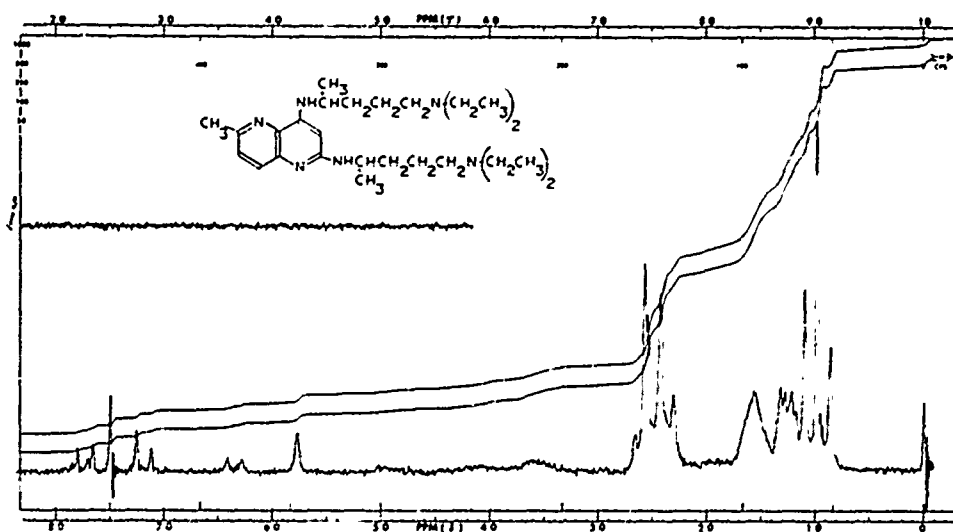
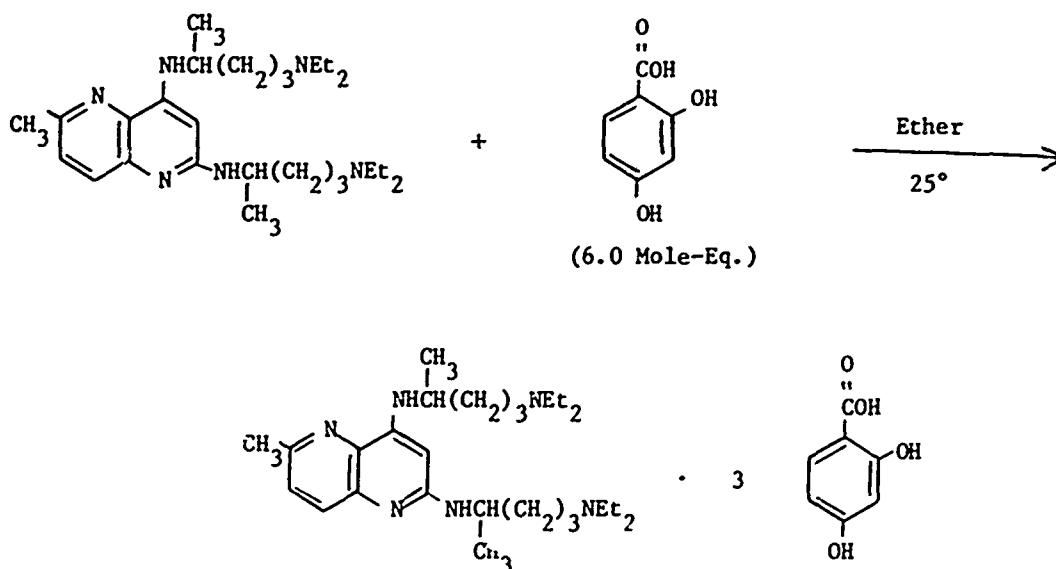


Figure 45. Proton spectrum of 2,4-di-(4-diethylamino-1-methylbutylamino)-6-methyl-1,5-naphthyridine (CDCl_3).

This 2,4-diamino derivative was submitted to WRAIR as the free base (amber oil). We have also prepared the β -resorcylate salt by the addition of an excess of 2,4-dihydroxybenzoic acid into an ether solution of the analytically pure free base.



The white solid which quickly separated was isolated by filtration and analyzed for the tri-β-resorcyate salt (Table 7). Its infrared spectrum is reproduced in Figure 46.

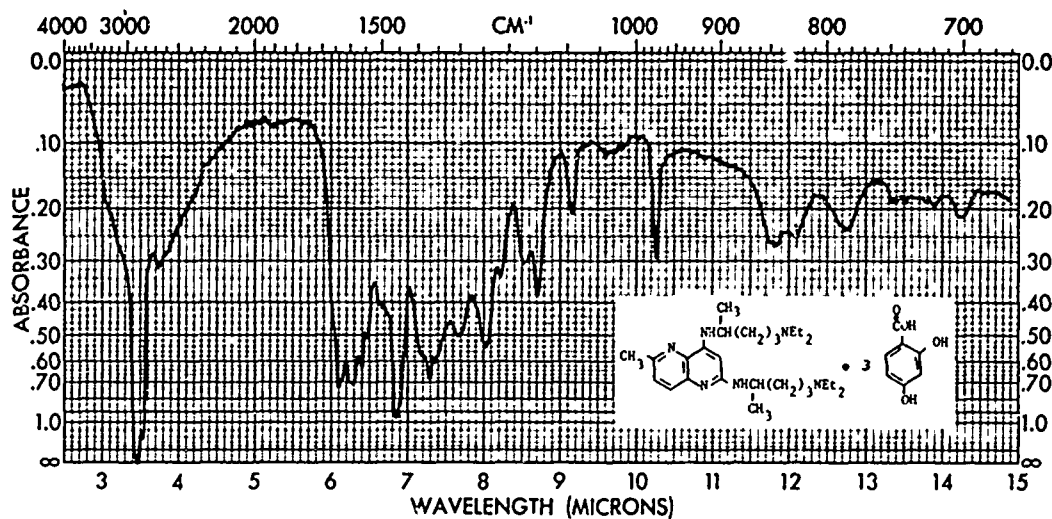


Figure 46. Infrared spectrum of 2,4-di-(4-diethylamino-1-methylbutylamino)-6-methyl-1,5-naphthyridine tri-β-resorcyate (nujol mull).

Table 7

4-Amino- and 2-Amino-1,5-Naphthyridines

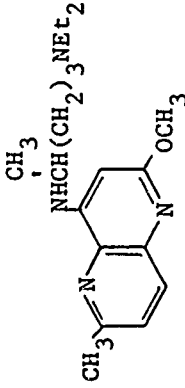
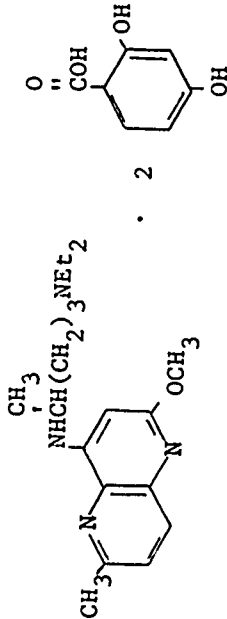
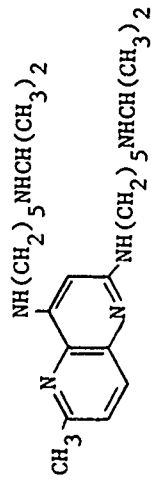
Structure	M.P., °C B.P., °C (mm)	Elemental Analysis			Theory Found
		C	H	N	
 (a)	145-170 (0.05 mm) (b)	69.05 69.39	9.15 9.61	16.96 17.10	
 (NT-22)	98-101	62.05 62.34	6.63 7.37	8.77 8.66	
 (NI-63)	43-45°	70.05 70.18	10.35 10.36	19.61 19.47	

Table 7 (Cont'd)
4-Amino- and 2-Amino-1,5-Naphthyridines

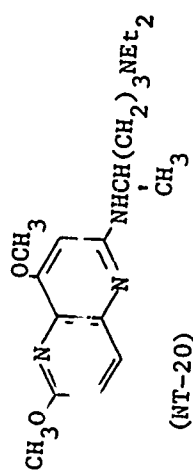
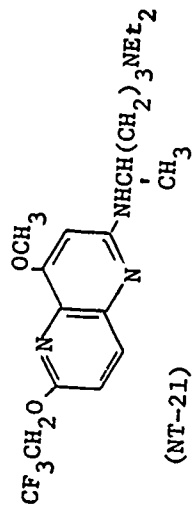
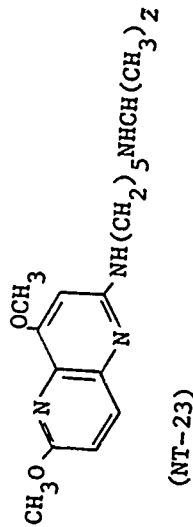
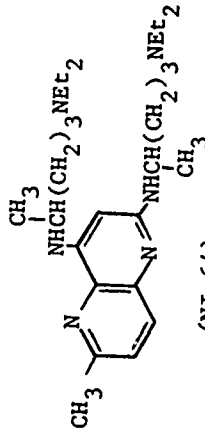
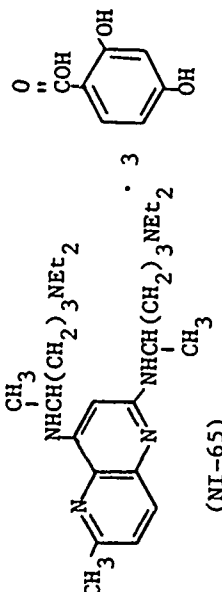
Structure	M.P., °C B.P., °C (mm)	Elemental Analysis			Theory Found
		C	H	N	
 (NT-20)	80-83	59.71 59.70	6.53 6.89	8.44 (c) 8.32	
 (NT-21)	97-100	56.50 56.19	5.72 6.12	7.75 7.69	
 (NT-23)	93-96	59.16 59.18	6.36 6.82	8.62 (c) 8.67	

Table 7 (Cont'd)

4-Amino- and 2-Amino-1,5-Naphthyridines

Structure	M.P., °C B.P., °C (mm)	Elemental Analysis		
		C	H	N
 (NI-64)	170-175 (0.02) ^(b)	71.00 71.36	10.59 10.40	18.40 18.54
				Theory Found
 (NI-65)	104-108	62.72 62.21	7.24 7.09	9.14 8.67

- (a) The free base was characterized, but not submitted for biologic testing.
 (b) Molecular distillation.
 (c) Hemi-hydrate.

3.5 Synthesis of Miscellaneous Intermediates

In conjunction with our other studies, a number of miscellaneous intermediates have also been characterized and submitted for biological testing this year. They are listed in Table 8 at the end of this section, and their preparative chemistry is discussed below.

The preparation of 6-benzyloxy-3-carboxy-4-hydroxy-1,5-naphthyridine, NI-47, was accomplished via hydrolysis of its 3-carbethoxy ester (NI-41, 12). The acid was isolated via our usual technique and it consistently analyzed as a hemi-hydrate (Table 8). Its infrared spectrum (Figure 47) is consistent with the formulated structure. We are presently attempting the decarboxylation of this acid as a route to the 6-benzyloxy target derivatives.

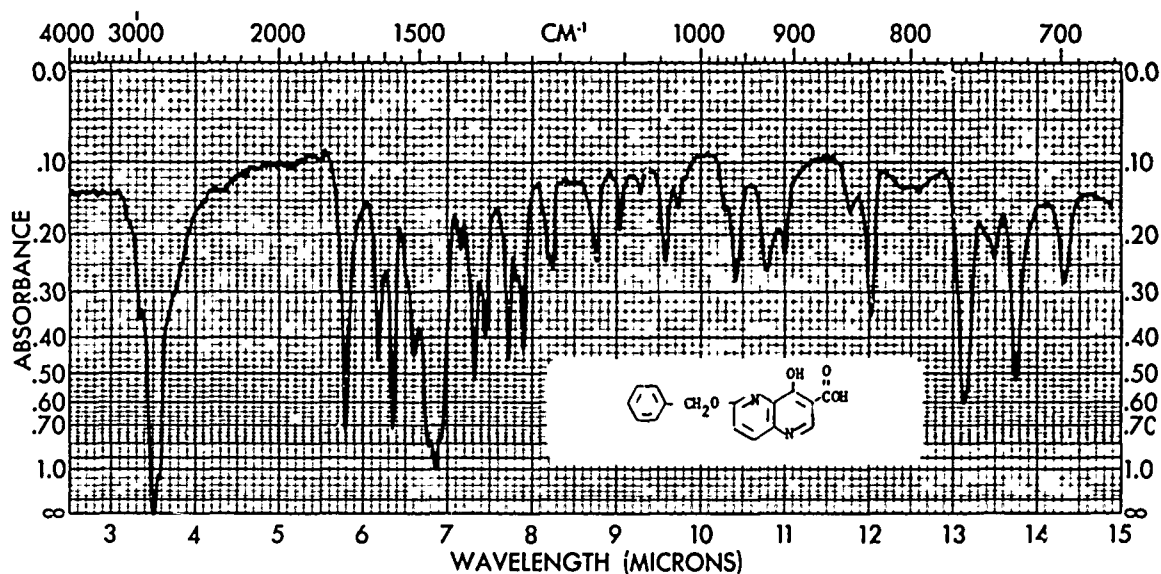
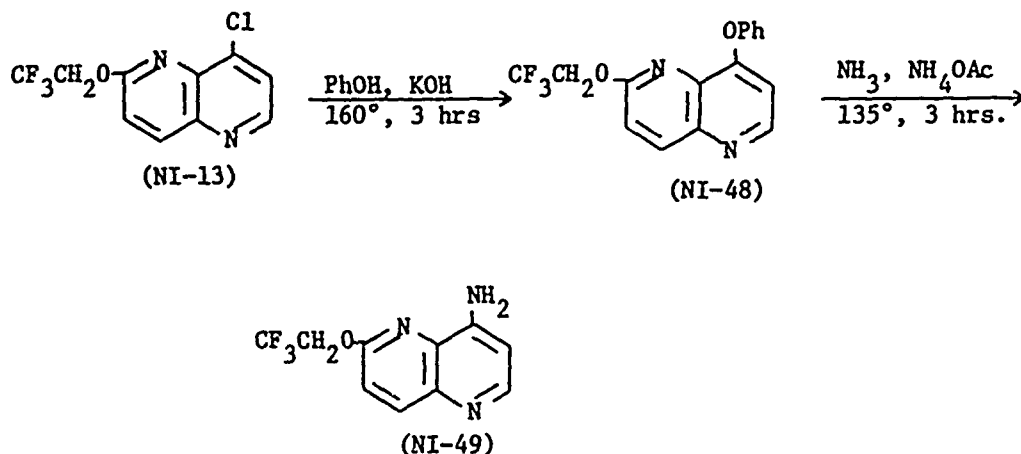


Figure.47. Infrared spectrum of 6-benzyloxy-3-carboxy-4-hydroxy-1,5-naphthyridine hemi-hydrate (nujol mull).

The two succeeding intermediates listed in Table 8 were prepared in conjunction with our studies directed at the inclusion of the primaquine side-chain onto the 4-position of the 1,5-naphthyridine ring. Reaction of 4-chloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (NI-13) with ammonia was attempted through the intermediacy of its 4-phenoxy derivative.



While the crude phenoxy derivative could be isolated in high yield, its reaction with ammonia was sluggish. Both the 4-amino analog (NI-49) and the 4-phenoxy compound (NI-48) were present in the final reaction mixture. Each of these products were isolated in pure form (Table 8), and the infrared spectrum for the 4-amino derivative is reproduced in Figure 48. It is our present contention that more forcing reaction conditions will have to be employed for the more efficient preparation of the 4-amino intermediate.

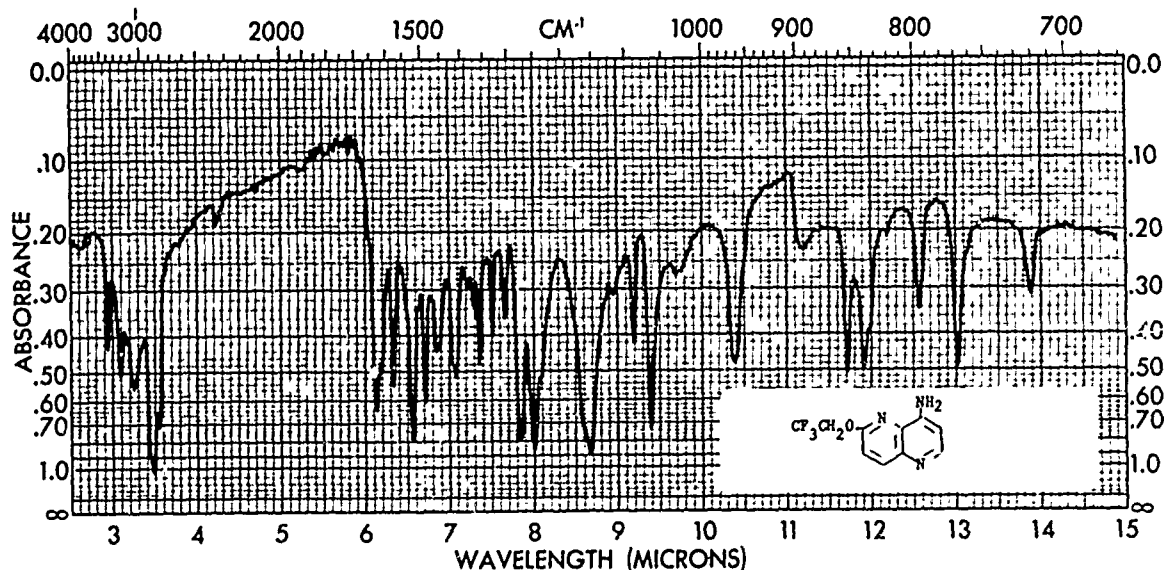


Figure 48. Infrared spectrum of 4-amino-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (nujol mull).

Both 2-amino-4-chloro-1,5-naphthyridine (NI-60) and 2,4-diphenoxy-1,5-naphthyridine (NI-61) were prepared as described in the literature (30). Their physical constants were virtually identical to that reported, and their infrared spectra are reproduced in Figures 49 and 50, respectively. We had initially sought their preparation as an alternative route to the desired 2-amino target structures. However, a more efficient route to the desired 2-amino target structures has been described in the preceding section. We have, therefore, discontinued any further work in this area.

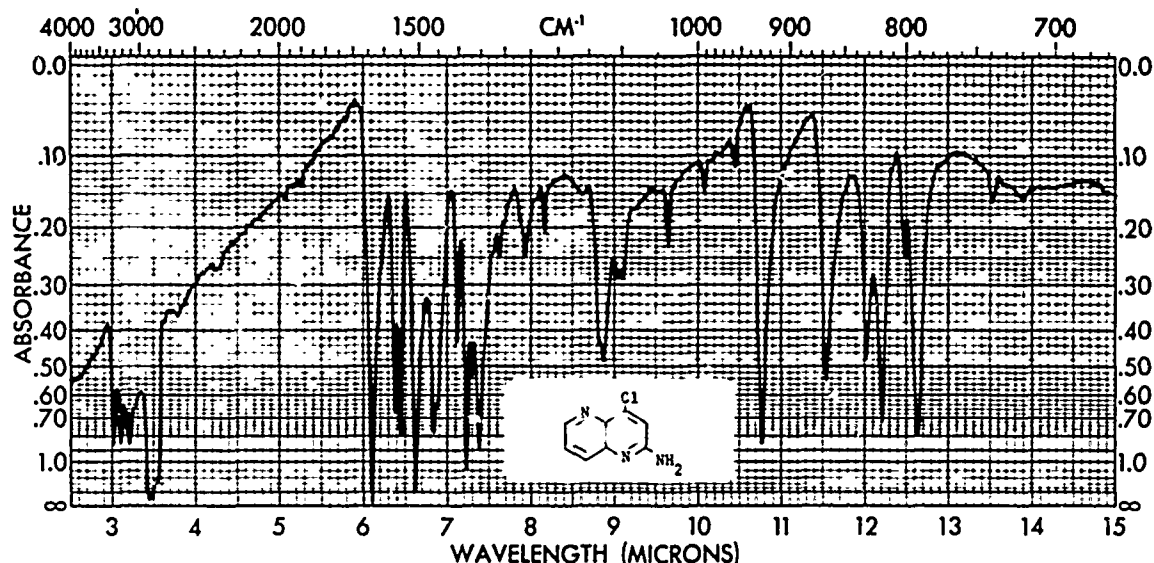


Figure 49. Infrared spectrum of 2-amino-4-chloro-1,5-naphthyridine (nujol mull).

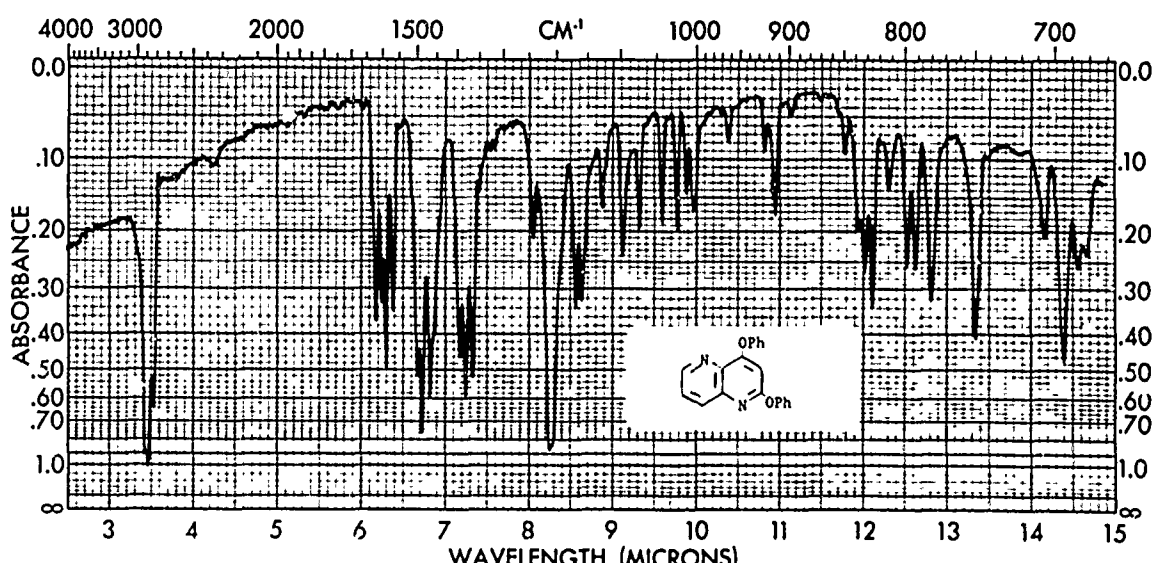
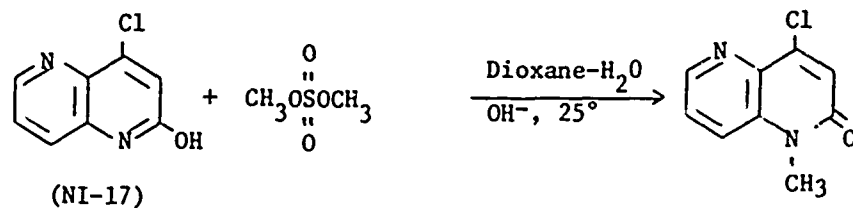


Figure 50. Infrared spectrum of 2,4-diphenoxy-1,5-naphthyridine (nujol mull).

The succeeding intermediate included in Table 8, 4-chloro-1-methyl-1,2-dihydro-1,5-naphthyridine-2-one (NI-62), was prepared as the immediate precursor to the N-methyl-2-keto-4-amino-1,5-naphthyridine analog specifically requested by WRAIR personnel. While the preparation of NI-62 has been previously reported in the literature (2), diazomethane must be employed, a mixture of isomers is produced, and the reaction is not suitable to scale-up. Accordingly, we have developed an alternative route as shown below.



The product as prepared via this route had physical properties identical to that reported in the literature (2), and it exhibited the predicted infrared and proton spectra (Figures 51 and 52).

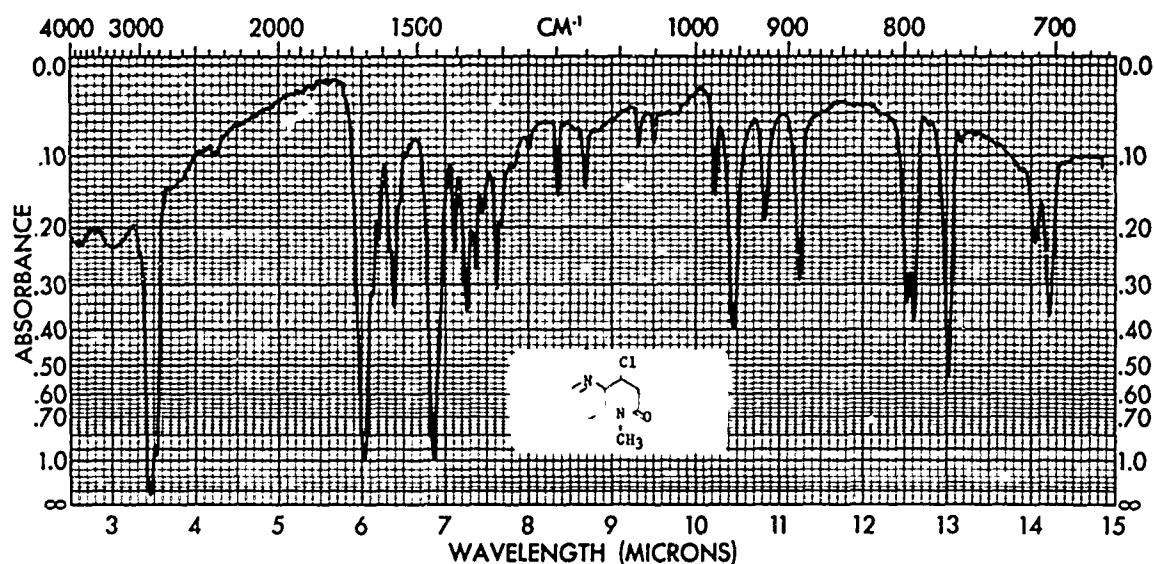


Figure 51. Infrared spectrum of 4-chloro-1-methyl-1,2-dihydro-1,5-naphthyridin-2-one (nujol mull).

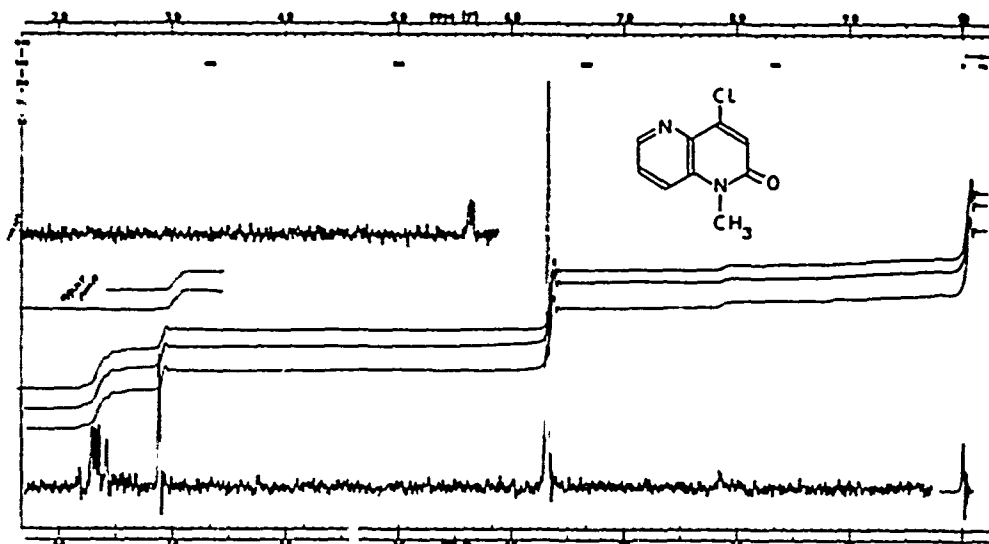
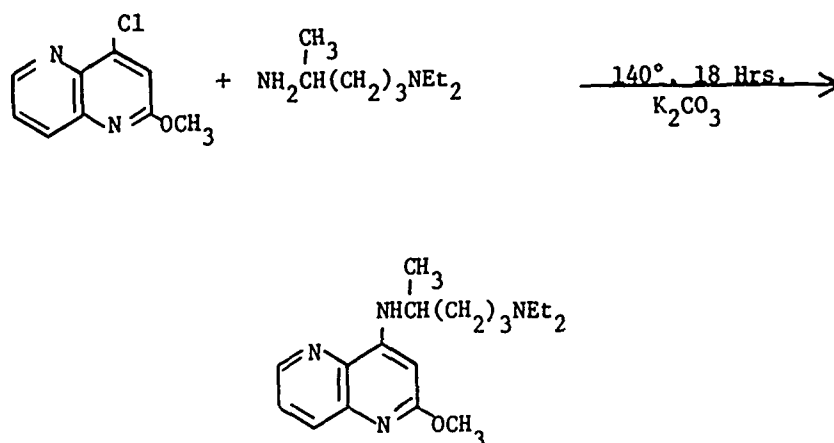


Figure 52. Proton spectrum of 4-chloro-1-methyl-1,2-dihydro-1,5-naphthyridin-2-one (CDCl_3).

As a second general approach to the synthesis of the desired N-methyl-2-keto-4-amino-1,5-naphthyridine, we have prepared 2-methoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine, NI-70, as described by Cheng (2).



The analytical data (Table 8) and proton spectrum (Figure 53) for this intermediate are in accord with Cheng's report (2). This intermediate was prepared, since Cheng reported a moderate translocation of the methyl group from the ether linkage to the ring nitrogen when the reaction was conducted in the presence of acid (2). We are presently reacting this intermediate (NI-70) with novaldiamine in the presence of 5 mole-eq. of novaldiamine dihydrochloride for extended periods of time. The results of these studies will be reported at a later date.

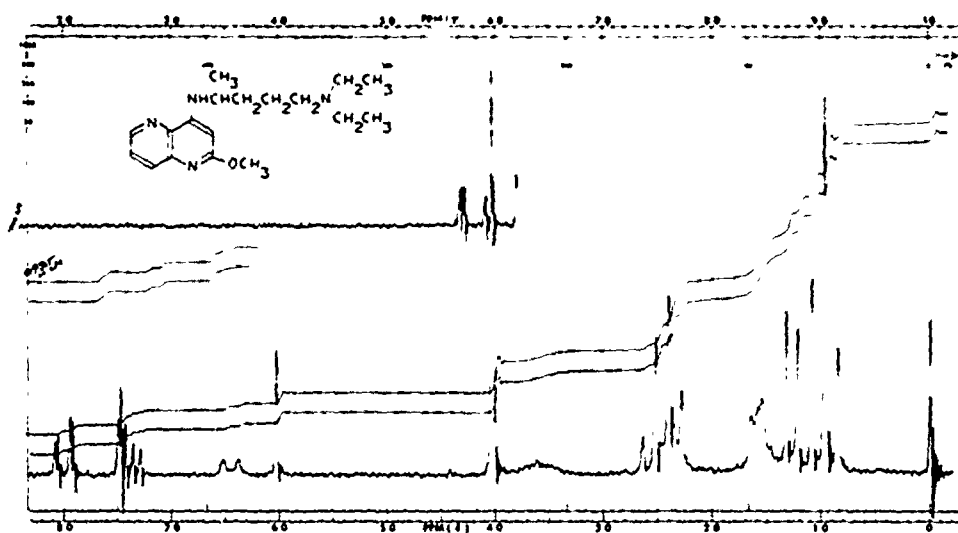


Figure 53. Proton spectrum of 2-methoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (CDCl_3).

Table 8

Miscellaneous 1,5-Naphthyridine Intermediates

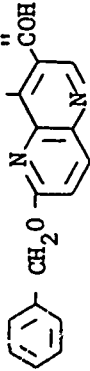
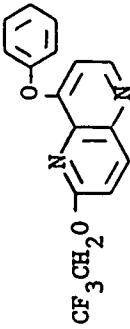
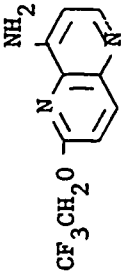
Structure	M.P., °C	Elemental Analysis			Theory Found
		C	H	N	
 (NI-47)	270-272	62.95 62.69	4.29 4.03	9.17 9.10	(a)
 (NI-48)	81-82	60.00 60.23	3.46 3.74	8.75 8.85	
 (NI-49)	164-165	49.39 49.50	3.31 3.22	17.28 17.11	

Table 8 (Cont'd)

Miscellaneous 1,5-Naphthyridine Intermediates

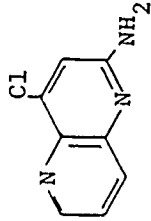
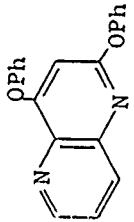
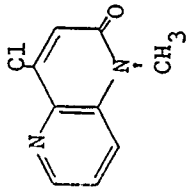
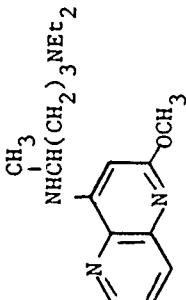
Structure	M.P., °C	Elemental Analysis			Theory Found
		C	H	N	
 (NI-60)	193-194	53.49 53.10	3.37 3.40	23.40 23.49	
 (NI-61)	174-176	76.42 76.44	4.49 4.59	8.91 8.94	
 (NI-62)	152-153	55.54 55.76	3.63 3.85	14.40 14.30	

Table 8 (Cont'd)

Miscellaneous 1,5-Naphthyridine Intermediates

Structure	M.P., °C B.P., °C (mm)	Elemental Analysis		
		C	H	N
	140-150 (0.06) (b)	68.32	8.92	17.71
		68.24	9.05	17.75
				Theory Found

(NI-70)

- (a) Hemi-hydrate.
(b) Molecular distillation.

4. EXPERIMENTAL

The experimental procedures used to prepare each of the precursors, intermediates and target 4-amino-1,5-naphthyridines which were submitted to WRAIR this year are explained in detail below. The synthetic procedures are listed numerically according to the code designation assigned to each compound. The Naphthyridine Precursors (NP-44 through NP-69), Naphthyridine Intermediates (NI- 42 through NI-72), and Naphthyridine Targets (NT-20 through NT-23) are included in Sections 4.3, 4.4 and 4.5, respectively.

4.1 Commercial Chemicals

All chemicals were of reagent grade and were purchased from a variety of commercial sources including Aldrich Chemical Company, Cedar Knolls, New Jersey; Eastman Kodak Company, Rochester, New York; Ace Scientific Supply Co., Inc., Linden, New Jersey; Matheson, Coleman and Bell East Rutherford, New Jersey; ICN-K&K Laboratories, Inc., Plainview, New York; PCR, Inc., Gainesville, Florida; Chemicals Procurement Laboratories, Inc., College Point, New York; Pfaltz and Bauer, Inc., Flushing, New York; Columbia Organic Chemicals Company, Inc., Columbia, South Carolina; Alfa-Ventron, Inc., Beverly, Massachusetts; J. T. Baker Chemical Company, Phillipsburg, New Jersey; and Matheson Gas Products, East Rutherford, New Jersey. All of the starting materials were used as received unless otherwise noted.

4.2 Physical, Spectral and Analytical Methods

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord Spectrophotometer (Model 137) using sodium chloride optics. Liquid samples were run as thin films and solid derivatives were run as nujol mulls versus air. Proton NMR spectra were determined with a Varian Associates A-60 spectrometer; samples were either run neat or in deuterio-chloroform solutions at room temperature. Chemical shift values are expressed in tau (τ) units versus internal tetramethyl silane as standard (10.0 τ). Refractive indices were carried out at 20-25° employing a thermostated Zeiss refractometer. Elemental analysis for carbon, hydrogen, nitrogen, chlorine and fluorine were performed by the Analytical and Information Division, Esso Research and Engineering Company, Linden, New Jersey.

4.3 Naphthyridine Precursors (NP-44 through NP-69)

6-Methylquinolinic Acid (NP-44)

In accord with the procedure as reported in the literature (13,15) a solution of 8-hydroxy-2-methylquinoline (20.0g, 0.126 mole) in 75 ml. of carbon tetrachloride was added very slowly into 100 ml. of fuming nitric acid (90%) at 0-5°. When the addition was completed, the mixture was slowly warmed and was allowed to stir at room temperature overnight. The red-brown solution was then slowly heated to 75-85° at which point a nitrogen purge was started to aid in the evolution of the brown fumes. The solvent was slowly evaporated until the volume was reduced to about 50 ml. After cooling to room temperature, 300 ml. of water was added and a small amount of insoluble yellow solid was removed by filtration. The water was removed on a rotary evaporator to afford a thick red-brown gum. The gum was taken up in 25 ml. of ethanol, and 100 ml. of ether was added dropwise with efficient stirring. A gummy oil separated which gradually formed a yellow suspension after stirring for several hours. Analytically pure 6-methylquinolinic acid was then isolated as a yellow powder in 48% yield (11.0g) after filtration, washing with ether and drying at 80° under reduced pressure. The infrared spectrum is reproduced in Figure 1, and the analytical data are included in Table 1.

6-Methylquinolindiamide (NP-45)

Diethyl 6-methylquinolinate was first prepared via the following procedure. Concentrated sulfuric acid (30g) was slowly added to absolute ethanol (30g) with cooling. Previously formed 6-methylquinolinic acid (12.0g, 66.2 mmole, NP-44) was then added slowly as a solid at room temperature. The mixture was slowly brought to 95° and was maintained at that temperature for four hours. The resultant dark brown solution was cooled to room temperature and was hydrolyzed by slowly adding into 300g. of ice water. The pH was adjusted to 8 by the addition of concentrated ammonium hydroxide. The mixture was then extracted five times with 150 ml. of ether. The combined ether layers were dried (MgSO₄) and the solvent removed to afford the crude ester as a dark brown oil in 64% yield (10.0g).

Crude diethyl 6-methylquinolinate (12.5g, 58.2 mmole) was then suspended in 120 ml. of concentrated ammonium hydroxide at room temperature. Gaseous ammonia was bubbled through the mixture for about five hours. A suspension formed which was filtered to afford crude product as a light tan solid in 58% yield (6.1g) after air drying. The analytical sample (Table 1) was obtained as a white solid after recrystallization from methanol (charcoal). The infrared spectrum for this precursor is reproduced in Figure 2.

6-Methylquinolinimide (NP-46)

Preformed 6-methylquinolindiamide (8.5g, 47.6 mole, NP-45) was placed in a 100 ml., one neck flash surrounded by an oil bath at room temperature. The temperature of the oil bath was slowly raised and the evolution of ammonia was monitored with wet pH paper. Very little ammonia was given off until the oil bath had reached 230°. After remaining at 230-235° for twenty minutes, the ammonia evolution ceased, and the initial white solid had converted into a brown solid. After cooling, the yield of crude imide was 94% (7.2g). The infrared spectrum of the crude imide was superimposable upon that of an analytical sample (Figure 3) which was isolated as an off-white solid after recrystallization from ethyl acetate and drying at 80°. The analytical data are included in Table 1.

3-Amino-6-methylpicolinic acid (NP-47)

A solution of sodium hypobromite was freshly prepared by the dropwise addition of bromine (12.3 ml.) into an ice-cold solution of sodium hydroxide (264 ml. of 2N). The hypobromite solution was kept cold and was immediately added dropwise into a solution of preformed 6-methylquinolinimide (35.2g, 0.218 mole, NP-46) in 660 ml. of 2N sodium hydroxide at 5°. The solution was stirred an hour at room temperature and an additional hour at 80° before cooling to room temperature. The mixture was then brought to a pH of 5 with 50% sulfuric acid and was left in the refrigerator overnight. The precipitated sodium sulfate was removed by filtration. A solution of cupric acetate (13.2g) and acetic acid (13.2 ml.) in 330 ml. of water was then added dropwise into the well-stirred filtrate. The copper salt of 3-amino-6-methylpicolinic acid was then isolated by filtration. The crude copper salt was suspended in water (ca., 500 ml.) and gaseous hydrogen sulfide was bubbled through the suspension for about two hours. The copper sulfide was removed by filtration. The filtrate and combined hot water wash of the filter cake was treated with charcoal and refiltered. Removal of the water under a strong nitrogen stream afforded the crude 3-amino-6-methylpicolinic acid in 84% yield (27.8g). An analytical sample (Table 1) was prepared by recrystallization from warm water and drying at 100° (0.10 mm). The infrared spectrum for the pure acid is reproduced in Figure 4.

Ethyl 3-amino-6-methylpicolinate (NP-48)

Concentrated sulfuric acid (55g) was slowly added into absolute ethanol (55g) at 10°. Preformed 3-amino-6-methylpicolinic acid (22.0g, 0.145 mole, NP-47) was then slowly added as a solid to the cool solution. The mixture was then heated to 95-100° for a total of four hours. The brown solution was then cooled and slowly poured into ca., 500g. of ice-water with efficient stirring. Concentrated ammonium hydroxide was added until the mixture attained a pH of 8-9. The aqueous suspension was then extracted three times with ether. The combined ether solutions were dried over magnesium sulfate and the solvent was removed to afford the crude ester in 28% yield (7.2g). An analytical sample (Table 1) was prepared by recrystallization from ether-heptane and drying under reduced pressure at 25°. The proton spectrum for this ester is reproduced in Figure 5.

Ammonium 3-carboxamido-6-methoxypicolinate (NP-49)

Our previously characterized dimethyl 6-methoxyquinolinate (42.0g, NP-36) was suspended in 1.4ℓ of concentrated ammonium hydroxide at room temperature. The suspension was stirred at 25° overnight before filtering. The filtered product (8.8g) proved to be our previously characterized 6-methoxyquinolindiamide (NP-37). An additional 2.2g of NP-37 was obtained by concentrating the filtrate to about 1ℓ. The water was then slowly removed from the filtrate over a period of several days by means of a nitrogen purge. A residual white solid was thereby obtained (26.9g) which proved to be the crude title product. The analytical sample (Table 1) was obtained by recrystallization from methanol-ether. Note: it was observed that this salt was quantitatively converted into our previously characterized 6-methoxyquinolinimide (NP-38) upon pyrolysis at 180-190°. The NP-38 thus obtained exhibited physical and spectral properties identical to authentic NP-38 obtained from pyrolysis (210-220°) of 6-methoxyquinolindiamide (NP-37).

Ammonium 6-methylquinolinate (NP-50)

Preformed 6-methylquinolinic acid (1.0g, NP-44) was added all at once to 50 ml. of concentrated ammonium hydroxide at room temperature. After stirring for two hours, the solvent was removed under a strong nitrogen stream. The residual solid was dried at 100° (0.10 mm) and analyzed correctly for the formulated structure (Table 1).

5-Nitro-2-picoline (NP-51)

As reported in the literature (23), sodium (18.0g, 0.784 mole) was dispersed in xylene (400 ml.) by heating the mixture to 125°, stirring at high speed for thirty seconds, and then allowing the dispersion to cool to room temperature without stirring. Diethyl malonate (124.0g, 0.773 mole) was then added dropwise with stirring while maintaining the temperature at 30°. The gelatinous mixture was then allowed to stand at room temperature for three days. Commercially available 2-chloro-5-nitropyridine (124.0g, 0.783 mole) was then added portionwise and the mixture was warmed to 110° with stirring for one and one-half hours. The mixture was then poured into one liter of 50% sulfuric acid. The xylene layer was separated and discarded. The aqueous phase was diluted with 500 ml. of water and re-fluxed for seven hours. The mixture was then made basic with 50% sodium hydroxide (about 1.2ℓ), and repeatedly extracted with ether. The ether extracts were combined and the solvent removed to afford the crude product as an amber solid in 23% yield (29.7g). An analytical sample (Table 2) was obtained as pale amber crystals by sublimation at 55-60° (0.06 mm).

Ethyl 6-methylnicotinate (NP-52)

Ethanol (105 ml.) was added dropwise into concentrated sulfuric acid (78 ml.) at 10° with efficient stirring. Commercially available 6-methylnicotinic acid (50.0g, 0.364 mmole) was then added portionwise at 10°. The suspension was heated to 80-90° for a total of four hours. The mixture was cautiously poured onto about 500g of ice with stirring. Aqueous sodium hydroxide solution (50%, ca., 200g) was then added dropwise until the pH was exactly neutral. The mixture was then extracted twice with 500 ml. of chloroform. The chloroform layers were combined, dried over magnesium sulfate and the solvent removed to afford crude product as a pale amber liquid of high purity in 75% yield (45.0g). The pure product was obtained as a colorless liquid in 71% yield by short path distillation (42.7g, b.p. 119-120°/16 mm). The analytical data are included in Table 2, and its proton spectrum is reproduced in Figure 8.

6-Methylnicotinamide (NP-53)

As described in the literature (14), preformed ethyl 6-methylnicotinate (40.0g, 0.242 mmole, NP-52) was stirred at room temperature and concentrated ammonium hydroxide (400 ml.) was quickly added. The oily dispersion cleared after three hours, and a white suspension formed after four hours. After stirring at room temperature overnight, crude product was isolated as a white solid in 73% yield (23.9g). An analytical sample (3.7g, Table 2) was obtained as colorless needles by recrystallization of the crude product (5.0g) from 150 ml. of hot water.

5-Amino-2-picoline (NP-54)

Preformed 5-nitro-2-picoline (21.0g, 0.152 mole, NP-51) in 150 ml. of methanol was added as a slurry into a refluxing mixture of reduced iron powder (50.5g) and acetic acid (2.1 ml.) in methanol-water (64 ml. each). The mixture was then refluxed overnight. At this point, a black mirror still was not present on the walls of the flask which usually serves as an indication of the completion of the reaction. More acetic acid (8 ml.) and i.c. (20.0g) was added and a black sheen gradually started to appear. After refluxing for an additional day, 20% sodium hydroxide was added (30 ml.), and the mixture was filtered. The filter cake was slurried with hot methanol, filtered, and this filtrate added to the first filtrate. A nitrogen purge was applied to the filtrates overnight to remove the methanol. The residual water layer was then extracted four times with chloroform. After drying (MgSO₄), the chloroform was removed to afford crude product as a brown solid in 61% yield (10.0g). The analytically pure amine was isolated as pale amber crystals by sublimation at 60° (0.05 mm). The analytical data are included in Table 2 and the proton spectrum is reproduced in Figure 9.

Diethyl 6-methyl-3-pyridylamino-
methylenemalonate (NP-55)

A sample of sublimed 5-amino-2-picoline (22.5g, 0.208 mole, NP-54) was slowly added as a solid into neat diethyl ethoxymethylene-malonate (45.0g, 0.208 mole) at room temperature with efficient stirring. Only a slight exotherm to 32° was noted during this addition. The mixture was then heated to 100° for one hour to drive the reaction to completion. The ethanol produced in this condensation was allowed to escape through a short air condenser. After cooling to room temperature, a crystalline solid quickly formed (m.p., 78-79°). This solid was recrystallized from 500 ml. of hot heptane to afford pure product (Table 4) as almost colorless crystals in 100% yield (53.3g).

2-Amino-5-nitro-4-picoline (NP-56) and
2-Amino-3-nitro-4-picoline (NP-57)

in accord with the procedure as reported in the literature (27), 2-amino-4-picoline (65.0g, 0.60 mole) was added portionwise to concentrated sulfuric acid (570g) at 10-15°. The mixture was then cooled to 7-8°, and concentrated nitric acid (64.5g) was slowly added dropwise. After the addition was completed, the mixture was allowed to warm to room temperature and the stirring was discontinued. After standing overnight, the mixture was stirred for one hour at room temperature and then slowly warmed to 95° for two hours. The mixture was cooled and slowly poured onto ca., 2000g of ice with efficient stirring. The mixture was then basified with concentrated ammonium hydroxide (ca., 780 ml.), and the resultant suspension was filtered to afford a mixture of the 3- and 5-nitro isomers in a combined yield of 92% (84.0g). This crude product was then suspended in about 750 ml of water and steam distilled. The distillation was continued until the initial bright yellow color of the distillate had faded to near colorless. The non-volatile component (5-nitro isomer, NP-56) was isolated by filtration as a tan solid in an overall yield of 44% (40.0g). The infrared spectrum of this crude product was identical to that of the analytically pure 5-nitro isomer (Figure 10) which was obtained by recrystallization from methanol. The analytically pure 3-nitro isomer (NP-57) separated from the cooled distillates and was isolated as a yellow crystalline solid in an overall yield of 13% (11.5g). The analytical data for both of these precursors are included in Table 2, and the infrared spectrum of NP-57 is reproduced in Figure 11.

2-Hydroxy-5-nitro-4-picoline (NP-58)

As previously described in the literature (27), preformed 2-amino-5-nitro-4-picoline (20.0g, 0.190 mole, NP-56) was dissolved in a mixture of concentrated sulfuric acid (22.2 ml) and water (318 ml). After stirring for a short period, a small amount (ca., 3g) of the unarranged nitramine was removed by filtration and discarded. The solution was then cooled to 7° and a cooled solution of sodium nitrite (12.7g, 0.184 mole) in 38 ml of water was added dropwise. The mixture was stirred for an additional hour at 5-10° and was then filtered. The crude 2-hydroxy-5-nitro-4-picoline was thereby isolated as a tan solid in 49% yield (14.0g, m.pt., 189-190°). The analytically pure material was prepared by recrystallization from ethanol (charcoal). The analytical data are included in Table 2 and its infrared spectrum is reproduced in Figure 12.

2-Chloro-5-nitro-4-picoline (NP-59)

As reported in the literature (28), 2-hydroxy-5-nitro-4-picoline (20.0g, 0.130 mole, NP-58), was slowly added as a solid into 160 ml. of phosphorous oxychloride at room temperature. The slurry was then heated on a steam bath for a total of 2.5 hours. The dark solution was cooled to room temperature and the excess phosphorous oxychloride was removed by vacuum distillation. The residue was then cautiously hydrolyzed by the dropwise addition of ca., 100 ml. of water with efficient stirring. The mixture was then extracted three times with ca., 100 ml. of ether. The combined ether layers were dried over magnesium sulfate and the ether was removed under a nitrogen stream. The residue was then subjected to a vacuum distillation to afford the analytically pure 2-chloro-5-nitro-4-picoline (NP-59) as an amber oil in an overall yield of 70% (15.7g, b.pt., 114-116°/6 mm, $n_D^{22.5}$ 1.5709). After standing overnight at room temperature, this precursor slowly crystallized to a low melting solid. The analytical data for this precursor are included in Table 2.

2-Methoxy-5-nitro-4-picoline (NP-60)

Preformed 2-chloro-5-nitro-4-picoline (38.9g, 0.225 mole, NP-59) was slowly added into a solution of sodium methoxide (48.8g of a 25% methanolic solution, one mole-eq.) in 800 ml. of methanol at room temperature. The mixture was then refluxed for five hours before filtering hot. The filtrate was then concentrated and cooled by means of a nitrogen purge. The resultant slurry was filtered to afford the crude 2-methoxy-5-nitro-4-picoline as an off white solid in an overall yield of 90% (36.2g, m.pt., 79-80°). The crude material analyzed correctly for the title product (Table 2).

5-Amino-2-methoxy-4-picoline (NP-61)

As reported in the literature (29), preformed 2-methoxy-5-nitro-4-picoline (25.5g, 0.152 mole, NP-60) was slowly added as a solid into a refluxing mixture of iron powder (62.0g) and acetic acid (4.0 ml) in 190 ml. of ethanol and 190 ml. of water. The slurry was refluxed an additional two hours after the addition was completed. After cooling to room temperature, sodium bicarbonate (84.0g) was added with stirring, and the mixture was refluxed an additional 2.5 hours before filtering hot. The filtrate was combined with a hot ethanol extract of the filter cake, and the solution was blown down to dryness under a nitrogen purge. The residue was extracted three times with ca., 100 ml. of ether. The combined ether layers were dried over potassium carbonate and the ether was removed under a nitrogen purge. The crude product was thereby obtained as a white solid in an overall yield of 91% (19.0g, m.pt., 93-94°). The analytical sample was isolated as a colorless solid by recrystallization by hot heptane and exhibited a melting point which was identical to that of the crude amine. The analytical data are included in Table 2, and its proton spectrum is reproduced in Figure 13.

Diethyl 6-methoxy-4-methyl-3-pyridylaminometylenemalonate (NP-62)

Preformed 5-amino-2-methoxy-4-picoline (13.8g, 0.10 mole, NP-61) was slowly added as a solid into one mole equivalent of diethyl ethoxy-methylenemalonate (21.6g, 0.10 mole) with efficient stirring at room temperature. The thick slurry was then slowly heated to 105-110° and maintained at that temperature for a total of one hour. The ethanol which was produced in this condensation was allowed to escape through a short air condenser. The heating was discontinued, and the contents of the flask solidified near 60°. Approximately 1 l. of heptane was added and the suspension was heated at reflux until the crude product completely dissolved. The solution was filtered hot and the pure product separated as a white solid upon cooling to room temperature. The yield of this precursor was 92% (28.4g, m.pt., 92-94°). The analytical data are included in Table 4, and its proton spectrum is reproduced in Figure 21.

8-Hydroxy-4-methylquinoline (NP-63)

As described in the literature (19), o-aminophenol (110.2g, 1.0 mole of 99% pure material) was added portionwise as a solid at room temperature into 400 ml. of con. hydrochloric acid in a 5 liter, 4-neck reaction flask equipped with a condenser, thermometer, addition funnel, and mechanical stirrer. The resulting blue suspension was slowly heated to 100°, and an excess of methyl vinyl ketone (142g, 2.0 mole of 98.5% pure material) was slowly added dropwise over a period of 35 minutes. The color of the reaction mixture changed from dark blue to green to golden brown as the addition progressed. The solution was maintained at 100-120° for an additional six hours during which time a precipitate formed. After cooling to room temperature, the mixture was steam distilled for approximately 1-2 hours, and the distillates were discarded. Aqueous sodium hydroxide (175 ml. of a 50% solution) was slowly added, and the steam distillation was resumed. The crude product was isolated from both the cooled distillates and exit condenser as a pale tan crystalline solid. A low overall yield of crude product (37.5g, 24%, m.pt., 140-141°) was thereby obtained even after a prolonged steam distillation for several days. The analytically pure 8-hydroxy-4-methylquinoline was obtained as a colorless solid from hot heptane (m.pt., 140-141°). The analytical data are included in Table 1 and its infrared spectrum is reproduced in Figure 6.

4-Methylquinolinic Acid (NP-64)

As described in the literature (20), preformed 4-methyl-8-hydroxyquinoline (20.8g, 0.131 mole, NP-63) was slowly added as a solid into 100 ml. of fuming nitric acid at 10° with efficient stirring. The mixture was then allowed to warm to room temperature and was stirred for three days. The dark solution was then gradually warmed to 85° and maintained at that temperature for three hours. A nitrogen stream was initiated, and the reaction mixture was reduced to a volume of about 50 ml. After cooling to room temperature, 300 ml. of water was added, and a small amount (ca., 0.5g) of insoluble yellow solid was removed by filtration and discarded. The water was then removed from the filtrate on a rotary evaporator. The crude product was isolated in several crops as a white solid in 70% yield (16.7g, m.pt., 189-191°). After drying at 100° (0.10 mm) for one day, the second crop constituted the analytical sample. The analytical data are included in Table 1, and its infrared spectrum is reproduced in Figure 7.

2-Hydroxy-3-nitro-4-picoline (NP-65)

Preformed 2-amino-3-nitro-4-picoline (32.5g, 0.212 mole, NP-57) was dissolved in a mixture of water (517 ml.) and concentrated sulfuric acid (36.1 ml.) at 8°. A solution of sodium nitrite (20.7g, 0.30 mole) in 62 ml. of water was then added dropwise while maintaining the temperature at less than 10°. The suspension was stirred for an additional 1.5 hours at 10° before filtering while still cold. The crude product was thereby isolated as a yellow-tan solid in 92% yield (30.1g) after air drying. The analytically pure precursor was obtained as a yellow solid after recrystallization from ethanol (charcoal). The analytical data are included in Table 2, and its infrared spectrum is reproduced in Figure 14.

2-Chloro-3-nitro-4-picoline (NP-66)

As reported by Roe and Seligman (28) preformed 2-hydroxy-3-nitro-4-picoline (27.5g, 0.179 mole, NP-65) was slowly added as a solid into phosphorous oxychloride (ca., 150 ml.) at room temperature. The mixture was heated to 85° for three hours and then cooled. The excess phosphorous oxychloride was removed by means of a nitrogen purge, and the residue was cautiously hydrolyzed by the dropwise addition of about 100 ml. of water with efficient stirring. The resultant tan slurry was extracted with ether several times. The ether layers were combined, dried over magnesium sulfate and the solvent removed to afford a brown oil. This oil was repeatedly triturated with boiling heptane. The combined heptane layers were cooled and concentrated to afford a moderate yield of the title precursor as a white solid in several crops. The analytical sample was recrystallized from heptane, and the analytical data are included in Table 2.

4-Methylquinolinic anhydride (NP-67) and
4-Methylquinolinimide (NP-68)

Preformed 4-methylquinolinic acid (80.0 g, 0.441 mole, NP-64) was quickly added into 120 ml of acetic anhydride at room temperature. The suspension was slowly heated, and a vigorous, almost explosive, exotherm was noted near 70°. After this initially vigorous reaction had subsided, the heating was again continued. Acetic acid was slowly distilled from the mixture over a period of about three hours until the internal pot temperature had reached 160°. The resultant brown-black solution was cooled to 100° and 39 g of acetic anhydride was added. After cooling to room temperature, a thick suspension of the crude anhydride separated from solution. An aliquot of this suspension was filtered to afford the crude anhydride as a brown solid. This solid was washed several times with ether and then recrystallized from methylene chloride-carbon tetrachloride (charcoal) to afford the analytically pure anhydride (Table 1) as an off white crystalline solid. Acetamide (46.0 g), followed by acetic anhydride (40.0 g) was then quickly added into the remainder of the original reaction mixture. This suspension was then maintained at 120-125° for a total of eighteen hours. After cooling to room temperature, a suspension quickly formed which was filtered to afford the crude imide as a dark tan solid in an overall yield of 46% (33.0 g). The analytically pure imide was obtained as a white solid by recrystallization from acetic acid (Table 1).

3-Amino-4-methylpicolinic acid (NP-69)

A solution of sodium hypobromite was freshly prepared by the dropwise addition of bromine (10.9 ml) into a well stirred solution of two normal aqueous sodium hydroxide (230 ml) maintained at 0-5° with the aid of an external ice bath. The hypobromite solution was then added dropwise into a solution of 4-methylquinolinimide (31.0 g, 0.191 mole, NP-68) in 580 ml of two normal sodium hydroxide at 0-5°. The mixture was then warmed to room temperature for one hour, and then heated to 80° for an additional hour to complete the rearrangement. The dark brown solution was then cooled to room temperature, and was brought to a pH of 5 with 50% sulfuric acid. A solution of cupric acetate (11.6 g) and glacial acetic acid (11.6 ml) in 290 ml of hot water was then added dropwise over a period of about one hour. The copper salt which immediately separated from solution was then isolated by filtration as a tan solid in an overall yield of 56% (19.5 g). The crude copper salt was suspended in about one liter of water, and hydrogen sulfide was bubbled through this suspension for a total of three hours. The copper sulfide was then removed by filtration. The solvent was removed from the clear amber filtrate, and the crude acid was thereby obtained in an overall yield of 44% (12.7 g). The analytical sample was obtained as yellow needles by recrystallization from methanol (Table 1).

4.4 Naphthyridine Intermediates (NI-42 through NI-72)

2-Chloro-4,6-dimethoxy-1,5-naphthyridine (NI-42)

Our previously characterized 2,4-dichloro-6-methoxy-1,5-naphthyridine (2.50g, 10.9 mmole, NI-37) was added portionwise as a solid over a period of twenty minutes into a solution of one mole-equivalent of sodium methoxide (2.34g of a 25% methanol solution) in 100 ml. of methanol at room temperature. The suspension was stirred overnight at room temperature before refluxing for a total of 6.5 hours. The methanol was then removed by means of a nitrogen purge to afford a white solid. This solid was boiled with 200 ml. of heptane, treated with magnesium sulfate, and was filtered hot. The colorless filtrate was cooled to -20° and the resultant white precipitate (1.3g) was isolated by filtration. This solid proved to be only about 90% pure by inspection of its proton spectrum. Analytically pure product was isolated in 29% yield by recrystallization from 100 ml. of hot heptane (0.7 g, m.p., 156.0-157.5°). The analytical data are included in Table 6, and the proton spectrum is reproduced in Figure 38.

4-Chloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine-1-N-oxide (NI-43)

A solution of m-chloroperoxybenzoic acid (3.40g of 85% pure material, 16.8 mmole) in 100 ml. of chloroform was slowly added dropwise over a period of two hours into a solution of our previously characterized 4-chloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (4.0g, 15.2 mmole, NI-13) in 100 ml. of chloroform at room temperature. No exotherm or color change was apparent during this addition. The mixture was stirred for three days at room temperature at which point a yellow-amber solution was observed. The chloroform solution was washed four times with aqueous potassium carbonate (18g in 250 ml. of water), and the water phases were discarded. Removal of solvent from the chloroform layer afforded crude product as a white solid in a yield of 4.1g. Analytically pure product was then obtained as colorless microcrystals in 50% yield (2.1g) by recrystallization from chloroform (magnesium sulfate)-heptane. The analytical data are included in Table 5, and the proton spectrum is reproduced in Figure 24.

6-n-Butoxy-4-chloro-1,5-naphthyridine-1-N-Oxide (NI-44)

A solution of m-chloroperoxybenzoic acid (1.72g of 85% pure material) in 100 ml. of chloroform was added dropwise into a colorless solution of our previously characterized 6-n-butoxy-4-chloro-1,5-naphthyridine (2.0g, 8.47 mmole, NI-12) in 50 ml. of chloroform at room temperature. After stirring for two days at room temperature, the medium yellow solution was washed four times with aqueous potassium carbonate (40g in 250 ml. of water). The water layer was discarded, and the chloroform phase was concentrated to about 25 ml. The addition of 250 ml. of heptane, followed by cooling, led to the separation of crude product in 70% yield (1.5g) which was isolated as a beige solid. The analytical sample (0.8g) was obtained by a two-fold recrystallization from chloroform-heptane. The analytical data are included in Table 5, and the proton spectrum is reproduced in Figure 25.

2,4-Dichloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (NI-45)

Preformed 4-chloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine-1-N-oxide (2.80g, 10.1 mmole, NI-43) was slowly added as a solid into 70 ml. of phosphorus oxychloride at 25°. A slight exotherm to 32° was noted during this addition. The mixture was refluxed for a total of 4.5 hours. The excess phosphorus oxychloride was then removed from the pale amber reaction solution by means of a nitrogen purge. The resultant gum was cautiously hydrolyzed by the addition of 150g. of ice with efficient stirring. The white suspension was brought to a pH of 9-10 with concentrated ammonium hydroxide. Crude product was then isolated in nearly quantitative yield (2.8g) as a white solid. Analytically pure product was isolated in 61% yield (1.8g) as a fluffy white solid by recrystallization from heptane (charcoal, magnesium sulfate) at -20°. The analytical data are included in Table 5, and the proton spectrum is reproduced in Figure 27.

2-Chloro-4-methoxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (NI-46)

Preformed 2,4-dichloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (10.0g, 33.7 mmole, NI-45) was added all at once into a solution of sodium methoxide (7.28g of a 25% methanolic solution, one mole-equivalent) in 300 ml. of methanol at room temperature. The clear solution was refluxed for eight hours after stirring at room temperature for one hour. Solvent was then removed by means of a nitrogen purge to afford a white solid. This solid was heated with 400 ml. of heptane, and the inorganic salt was removed by filtration of the hot heptane suspension. The heptane filtrate was then heated to boiling, treated with magnesium sulfate and charcoal, and filtered hot. The clear, colorless filtrate was cooled to -20°, and analytically pure product was isolated by filtration as colorless needles in 48% yield (4.7g, m.p., 113-115°). The analytical data are included in Table 6, and the proton spectrum is reproduced in Figure 33.

6-Benzoyloxy-3-carboxy-4-hydroxy-1,5-naphthyridine hemi-hydrate (NI-47)

Previously characterized 6-benzoyloxy-3-carbethoxy-4-hydroxy-1,5-naphthyridine (57.0g, 0.176 mole, NI-41) was quickly added into 1.12% of one normal sodium hydroxide solution at room temperature. The suspension was then refluxed for a total of three hours. A small amount of insoluble material (3.0g) was removed by filtration, and the filtrate was brought to a congo red end point with concentrated hydrochloric acid. A thick suspension formed which was diluted with additional water before filtration. The crude acid was then isolated as an off-white solid in quantitative yield by filtration. An analytical sample (5.8g) was prepared by reprecipitation of the crude acid (6.3g) from 150 ml. of warm, one-normal sodium hydroxide with concentrated hydrochloric acid (congo red end-point). The acid was collected by filtration, washed well with water and dried at 110° (0.10 mm) for two days. The product consistently analyzed as a hemi-hydrate (Table 8). The infrared spectrum (Figure 47) was consistent with the formulated structure.

4-Phenoxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (NI-48)

A mixture of 4-chloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (18.0g, 68.5 mmole, NI-13), phenol (30.0g) and potassium hydroxide (4.4g) was heated to 160° for three hours with efficient stirring. The resultant orange, pasty liquid was poured into 500 ml. of two-normal sodium hydroxide. A gelatinous emulsion formed which was extracted three times with 150 ml. of ether. The combined ether layers were washed three times with dilute sodium hydroxide solution and finally with water. Removal of the ether afforded the crude phenoxy derivative as an oil. An analytical sample (Table 8) was prepared by recrystallization from ether-heptane and was isolated as a white solid. This phenoxy derivative was also the major product obtained after reaction with gaseous ammonia in an ammonium acetate flux at 135° for three hours.

4-Amino-6-(2,2,2-trifluoroethoxy)-
1,5-naphthyridine (NI-49)

Crude 4-phenoxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (NI-48) was prepared as described above starting from 18.0g of 4-chloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (NI-13). The crude phenoxy oil thus obtained (NI-48) was mixed with 100g of ammonium acetate and slowly warmed to 135°. Ammonia was bubbled through the mixture for a total of three hours. After cooling to room temperature, water (300 ml.) and glacial acetic acid (20 ml.) were added. The mixture was allowed to stand at room temperature overnight. A small amount of an oily, insoluble solid was precipitated which was removed by filtration. The filtrate was then made basic with about 30 ml. of ammonium hydroxide. A white suspension formed, which after filtration, afforded the crude 4-amino derivative in 17% yield (2.8g). The analytical sample was recrystallized from ether-heptane and was obtained as a white solid after drying under reduced pressure at 25°. The analytical data are included in Table 8, and the infrared spectrum is reproduced in (Figure 48).

2,4-Dihydroxy-6-methyl-1,5-
naphthyridine (NI-50)

Previously characterized ethyl 3-amino-6-methylpicolinate (9.0g, 49.9 mmole, NP-48) was added portionwise over a period of about twenty minutes into 100 ml. of diethyl malonate at 195°. After the addition was completed, the mixture was kept an additional thirty minutes at 195° to ensure the completion of the reaction. The mixture was then cooled to room temperature and the excess diethyl malonate was removed by distillation under reduced pressure. Ether (450 ml.) was then added to the residual dark, red-brown semi-solid and the mixture was stirred until almost all of the residue had dissolved. After removing a small amount of ether insoluble material by filtration (ca., 0.05g), the ether layer was returned to a 4-neck reaction flask. A solution of sodium ethoxide (4.32g, 6.35 mmole) in 50 ml. of absolute ethanol was then added dropwise into the ether layer with efficient stirring. A yellow-tan suspension immediately formed which was stirred at room temperature overnight. The suspension was then refluxed for six hours and filtered to afford an off-white solid. This solid was placed in a 500 ml. reaction flask, and water (20 ml.), followed by aqueous sodium hydroxide solution (35 ml. of a 50% solution), was slowly added with efficient stirring. The thick suspension was slowly warmed to 105-110° to effect the decarboxylation. After remaining at 105-110° for thirty minutes, 250 ml. of hot water was added and the thin suspension was kept at 90° for one hour. The mixture was then filtered while hot to remove the insoluble component. The clear amber filtrate was then brought to a pH of 5 with glacial acetic acid. The white suspension which formed was cooled to 15° before filtration to afford crude product as an off-white solid in 59% yield (5.2g). An analytical sample was prepared by recrystallization from hot water. The analytical data are included in Table 3, and the infrared spectrum is reproduced in Figure 15.

2,4-Dichloro-6-methyl-
1,5-naphthyridine (NI-51)

Our previously characterized 2,4-dihydroxy-6-methyl-1,5-naphthyridine (4.0g, 22.7 mmole, NI-50) was slowly added into phosphorus oxychloride (100 ml.) at 25°. A slight exotherm to 32° was noted with this addition. The suspension was then slowly brought to reflux and maintained at that temperature for four hours. The mixture was then cooled to room temperature and the excess phosphorus oxychloride removed under a nitrogen purge. The resultant red-brown gum was cautiously hydrolyzed by the dropwise addition of 125 ml. of water at 25-40°. Ammonium hydroxide was then added until a pH of 9 was attained. The suspension was then filtered to afford crude product as a rose colored solid (4.1g). The pure dichloro compound was obtained as a white solid in 60% yield (2.95g, m.p., 134-136°) by sublimation at 100-110° (0.04 mm). The analytical data are included in Table 3, and its proton spectrum is reproduced in Figure 16.

4-Chloro-2-methoxy-6-methyl-1,5-naphthyridine (NI-52)
and 2-Chloro-4-methoxy-6-methyl-1,5-naphthyridine (NI-53)

Analytically pure 2,4-dichloro-6-methyl-1,5-naphthyridine (2.13g, 10.0 mmole, NI-51) was slowly added as a solid into a solution of sodium methoxide (2.16g of a 25% solution in methanol, 1.0 mole - eq.) in 50 ml. of methanol at room temperature. The suspension was then immediately brought to reflux and maintained at that temperature for a total of 2.5 hours. The solvent was then removed under a nitrogen purge to afford a white solid. This solid was extracted with 100 ml. of boiling heptane. The inorganic salt was then removed by filtration (0.55g). After standing at room temperature for several hours, a crystalline solid separated from the heptane filtrate. This solid was isolated by filtration and proved to be 2-chloro-4-methoxy-6-methyl-1,5-naphthyridine (NI-53) which was isolated in 32% yield (0.67g, m.pt. 144.5-145.0°). Three successive crops of product were then obtained by partial removal of the heptane and cooling to about 5-10°. The second crop (0.24g) proved to be a mixture of both of the title products. The third and fourth crops (0.75 and 0.15g, 48%) proved to be the retroisomer (NI-52) which was isolated as a white solid. The third crop constituted the analytical sample of NI-52. The analytical data for both of these products are included in Table 6 and their proton spectra are reproduced in Figures 34 and 35, respectively.

3-Carbethoxy-4-hydroxy-6-methyl-
1,5-naphthyridine (NI-54)

Diethyl 6-methyl-3-pyridylaminomethylenemalonate (15.0g, 53.8 mmole, NP-55) was slowly added as a solid into refluxing diphenyl ether (250°) over a period of ten minutes. The mixture was maintained at reflux for an additional twenty minutes before cooling. Heptane was then added (200 ml.) and the slurry was stirred at room temperature for two hours before filtering. The crude product was thereby isolated as a grey solid in 42% yield (5.3g). This solid was repeatedly triturated with boiling ethanol to afford the analytically pure material (3.7g). The analytical data are included in Table 4, and its infrared spectrum is reproduced in Figure 17.

3-Carboxy-4-hydroxy-6-methyl-
1,5-naphthyridine (NI-55)

The preformed ester, 3-carbethoxy-4-hydroxy-6-methyl-1,5-naphthyridine (26.0g, 0.112 mole, NI-54), was added all at once into 500 ml. of 1N sodium hydroxide. The suspension was maintained at 85-90° for two hours at which point a clear, brown solution was present. The mixture was treated with charcoal and filtered while hot. The brown filtrate was then brought to a congo red end point with concentrated hydrochloric acid. The suspension was filtered to afford the crude acid as a tan solid in 65% yield (15.0g). Analytically pure product was obtained by dissolving the crude acid in 300 ml. of 1N sodium hydroxide, treatment with charcoal, and reprecipitation to a congo red end point with concentrated hydrochloric acid. After drying at 110° (0.10 mm), the overall yield of NI-55 was 57% (11.7g). The analytical data are included in Table 4, and the infrared spectrum is reproduced in Figure 18.

4-Hydroxy-6-methyl-1,5-
naphthyridine (NI-56)

Our previously characterized 3-carboxy-4-hydroxy-6-methyl-1,5-naphthyridine (11.7g, 57.2 mmole, NI-55) was added portionwise to 200 ml. of nujol at 295-300°. The appearance of a white sublimate was noted during this addition. Heating was continued for an additional fifteen minutes before cooling the mixture. An equal volume of heptane was then added with stirring. The crude product was then isolated as a tan solid in 93% yield (8.5g) by filtration. The analytical sample was obtained by recrystallization from methanol at -70°. The analytical data are included in Table 4, and the infrared spectrum is reproduced in Figure 19.

4-Chloro-6-methyl-1,5-naphthyridine (NI-57)

Crude 4-hydroxy-6-methyl-1,5-naphthyridine (7.0g, 43.4 mmole, NI-56) was slowly added into 100 ml. of phosphorus oxychloride at 25°. A moderate exotherm to 32° was noted during this addition. The suspension was then slowly warmed to reflux and maintained at that temperature for a total of four hours. The resultant deep, blue-black suspension was cooled to room temperature and the excess phosphorus oxychloride was removed under a strong nitrogen purge. The residual, blue-black gum was cautiously hydrolyzed at 25-40° by the dropwise addition of 100 ml. of water with mechanical stirring. The dark mixture was then brought to pH 8-9 with concentrated ammonium hydroxide. At this point, the reaction mixture consisted of a blue-black solution with a fair amount of blue-black tar adhering to the walls. The aqueous phase was separated and extracted twice with 400 ml. of ether. The adherent tar was also repeatedly triturated with warm ether. All of the ether phases were then combined, treated with magnesium sulfate and charcoal, and the solvent removed to afford crude product as an off-white solid in 63% yield (4.9g). An analytical sample (3.0g) was isolated as a white, crystalline solid by sublimation of 3.7g of the crude product at 75° (0.02 mm). It was noted that this chloro derivative gradually darkened to a grey solid upon storage. The analytical data are included in Table 4, and the proton spectrum is reproduced in Figure 20.

2-Chloro-4-methoxy-1,5-naphthyridine (NI-58)

Our previously characterized 2,4-dichloro-1,5-naphthyridine (1.99g, 10.0 mmole, NI-15) was added all at once into a solution of sodium methoxide (2.16g of a 25% solution in methanol, 1.0 mole-eq.) in 50 ml. of methanol at room temperature. The mixture was quickly brought to reflux and maintained at that temperature for a total of two hours. The solvent was then removed under a nitrogen stream, and the resultant white solid extracted with 75 ml. of boiling heptane. Magnesium sulfate was then added, and the mixture was filtered while hot. The solvent was then removed from the heptane solution, and the crude white solid was dried at 50° (0.10 mm) for eighteen hours. This solid analyzed correctly for the empirical formula $C_9H_7ClN_2O$:

Theory: C, 55.54; H, 3.63; N, 14.40.
Found: C, 55.46; H, 3.60; N, 14.30.

The overall yield of the crude product was 97% (1.90g). However, a prominent band was present near 11.1μ in the infrared spectrum. Also, the proton spectrum for this solid (Figure 29) revealed the presence of two discrete isomers. The title isomer, NI-58, was obtained as the first crop in low yield by recrystallization from warm heptane at room temperature. The proton spectrum for this analytically pure derivative (Table 6) is reproduced in Figure 30. The proton spectrum for its previously characterized retroisomer, NI-16, is reproduced in Figure 31. and clearly discloses that NI-16 is the second component present in the reaction mixture.

2-Chloro-4-methoxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (NI-46) and 4-Chloro-2-methoxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (NI-59)

Recrystallized 2,4-dichloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (30.0g, 0.101 mole, NI-45) was added all at once into a solution of sodium methoxide (21.8g of a 25% methanolic solution, one mole-eq.) in 300 ml. of methanol at room temperature. The clear solution was refluxed for eight hours after stirring at room temperature for one hour. Solvent was then removed by means of a nitrogen purge to afford a white solid. This solid was triturated with one liter of boiling heptane, treated with charcoal and magnesium sulfate and filtered hot. The heptane filtrate was allowed to stand at room temperature overnight. A white crystalline solid separated which was isolated in a yield of 11.8g. A second crop was isolated as a white solid in a yield of 7.2g after cooling the heptane filtrate to -20° overnight. Removal of solvent from the filtrate afforded the third crop (9.6g) as an off-white solid. The combined yields of all three crops were 28.6g (97%). The first crop was determined to be 2-chloro-4-methoxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (NI-46) by examination of its proton spectrum (Figure 33). An analytical sample of NI-46 (m.p., 113-115°) was obtained by recrystallization from heptane and exhibited a proton spectrum identical to the crude first crop. The second crop was judged to be a 90:10 mixture of NI-46 and its retroisomer, 4-chloro-2-methoxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (NI-59) by examination of its infrared spectrum. An analytical sample of the retro-

isomer, NI-59, was obtained by recrystallization of the third crop (9.6g, 70% retroisomer:30% NI-46 by its proton spectrum) first from 100 ml. of heptane at 0° (4.4g, 90% retroisomer by NMR) followed by a second recrystallization from 150 ml. of heptane at 0° (2.2g). The proton spectrum for this pure retroisomer (NI-59) is reproduced in Figure 34, and the analytical data are included in Table 6.

2-Amino-4-chloro-1,5-naphthyridine (NI-60)

Our preformed 2,4-dichloro-1,5-naphthyridine (4.0g, 20.1 mmole, NI-15) was placed in a rocker, pressure bomb with 100 ml. of ammonia saturated ethanol. The temperature was raised to 150° (pressure 275-340 psig) and the mixture was agitated overnight. The reaction mixture was then transferred to an Ehrlenmeyer flask and the solvent was removed by means of a nitrogen stream. The residual yellowish solid was repeatedly washed with water and then dried under reduced pressure. The yield of crude product was 83% (3.0g). Analytically pure product was then obtained as a white powder by sublimation at 130-145° (0.05 mm). The analytical data are included in Table 8, and its infrared spectrum is reproduced in Figure 49.

2,4-Diphenoxy-1,5-naphthyridine (NI-61)

As reported in the literature (30), a mixture of 2,4-dichloro-1,5-naphthyridine (2.0g, 10.0 mmole, NI-15) and an excess of phenol (60.0g) was refluxed for six hours at 185°. The mixture was then treated with the theoretical quantity of sodium hydroxide (256g. of a 10% solution) and stirred for about an hour. A crystalline solid formed which was filtered and air dried overnight. The yield of crude product was 95% (3.0g). An analytical sample was prepared by recrystallization from hot heptane and vacuum drying at 50°. The analytical data are included in Table 8, and the infrared spectrum is reproduced in Figure 50.

4-Chloro-1-methyl-1,2-dihydro-1,5-naphthyridine-2-one (NI-62)

Preformed 4-chloro-2-hydroxy-1,5-naphthyridine (2.02g, 12.2 mmole, NI-17) was added all at once into a mixture of water (25 ml.) and dioxane (20 ml.) at room temperature. A solution of one mole-equivalent of sodium hydroxide (0.98g of a 50% aqueous solution) in 5 ml. of water was then added dropwise. The suspension gradually cleared to form a medium amber solution at the end of the addition. Dimethyl sulfate (0.768g, 6.1 mmole) was then added over a period of ten minutes and the mixture was stirred at room temperature overnight. The solvent was then removed to afford a yellowish, gummy solid. This solid was repeatedly extracted with 80 ml. of heptane (five times) and finally with 300 ml. of heptane. Crude product was then isolated as a white solid in 55% yield (1.3g) by removal of the heptane under a nitrogen purge. Analytically pure product (0.8g, Table 8) was obtained as a white crystalline solid by recrystallization from heptane. The infrared and proton spectra are reproduced in Figures 51 and 52, respectively.

2,4-Di-(5-isopropylaminopentylamino)-6-methyl-1,5-naphthyridine (NI-63)

A mixture of our previously characterized 4-chloro-2-methoxy-6-methyl-1,5-naphthyridine (3.40g, 16.3 mmole, NI-52), 5-isopropylaminopentylamine (10.0g, 69.5 mmole, 41), and a catalytic quantity of copper-bronze (0.5g) was slowly brought to 170-180° and maintained at that temperature for a total of twenty-four hours. After cooling to room temperature, the brown semi-solid was thoroughly mixed with 50 ml. of 5 N sodium hydroxide. The upper oily phase was then extracted into 75 ml. of ether. A second ether extract of the water phase led to a cloudy ether extract. This second ether extract was filtered to afford a white solid (ca., 0.3g) which has not as yet been characterized. Both ether phases were combined, dried over magnesium sulfate, and the solvent removed to afford an amber, oily suspension. This suspension was taken up in 100 ml. of heptane and cooled to -20° overnight. The resultant suspension was filtered to afford a second crop of the insoluble component (ca., 0.5g). The heptane was then removed from the filtrate to afford an amber oil which was subjected to a molecular distillation. After the removal of excess diamine, very little distillate was collected until the temperature rose to 160°. A small amount of distillate (0.3g, yellow liquid) was collected at 150-160°/0.02 mm. A proton spectrum of this liquid revealed it to be a 50:50 mixture of the title product and the expected mono-4-amino product. After a small intermediate cut, the title product was then isolated as an amber oil in 31% yield (170-180°/0.02 mm). After several days, this oil slowly formed a solid which melted at 43-45°. The analytical data are included in Table 7, and its proton spectrum is reproduced in Figure 41.

2,4-Di-(4-diethylamino-1-methylbutylamino)-6-methyl-1,5-naphthyridine (NI-64)

A mixture of our previously characterized 2-chloro-4-methoxy-6-methyl-1,5-naphthyridine (2.0g, 9.60 mmole, NI-53), 2-amino-5-diethylaminopentane (15.0g, 94.5 mmole), and a catalytic quantity of copper-bronze was slowly raised to 165-170° and maintained at that temperature for a total of eighteen hours. After cooling to room temperature, 50 ml. of 5 N sodium hydroxide was added and the two phase system was thoroughly mixed. The upper oily phase was extracted with ether (75 ml., three times). The ether layers were combined, dried over magnesium sulfate and the solvent removed under a nitrogen purge. The residual brown liquid was then subjected to a molecular distillation. After the removal of excess diamine, very little distillate was collected until the temperature rose to 170°. The title product was then isolated as a yellow-amber oil in an overall yield of 66% (2.9g, 170-175°/0.02 mm). The analytical data are included in Table 7, and its proton spectrum is reproduced in Figure 45.

2,4-Di-(4-diethylamino-1-methylbutylamino)-6-methyl-1,5-naphthyridine tri- β -resorcylate (NI-65)

A solution of 2,4-dihydroxybenzoic acid (3.56g, 22.4 mmole, 6.0 mole-eq. of 97% pure material) in 100 ml. of ether was added dropwise into a solution of 2,4-di-(4-diethylamino-1-methylbutylamino)-6-methyl-1,5-naphthyridine (1.7g, 3.72 mmole, NI-64) in 200 ml. of ether at room temperature. A white suspension formed immediately which was stirred for two hours before filtering a nearly quantitative yield of product (3.30g). The product was repeatedly washed with ether and was dried at 25° under high vacuum. The analytical data are included in Table 7, and its infrared spectrum is reproduced in Figure 46.

4-Chloro-6-methyl-1,5-naphthyridine-1-N-oxide (NI-66)

A solution of m-chloroperoxybenzoic acid (3.25g, 16.0 mmole, 1.1 mole-eq. of 85% pure material) in 100 ml. of chloroform was slowly added dropwise into a solution of 4-chloro-6-methyl-1,5-naphthyridine (2.60 g, 14.6 mmole, NI-57) in 100 ml. of chloroform at room temperature. The clear yellow solution was stirred at room temperature for five days before transferring to a separatory funnel and washing three times with aqueous potassium carbonate (20 g in 300 ml. of water). The clear yellow chloroform solution was dried over magnesium sulfate and the solvent removed to afford a pale yellow-tan solid. The proton spectrum for this crude product which was isolated in 85% yield (2.40g) was identical to that of the analytically pure material isolated by recrystallization from chloroform-heptane. The analytical data are included in Table 5, and its proton spectrum is reproduced in Figure 23.

3-Carbethoxy-4-hydroxy-6-methoxy-8-methyl-1,5-naphthyridine (NI-67)

Diethyl 6-methoxy-4-methyl-3-pyridylaminomethylenemalonate (10.0g, 32.4 mmole, NP-62) was slowly added as a solid into refluxing diphenyl ether (100 ml, 250°). The solution was maintained at reflux for an additional two hours before cooling to room temperature. Heptane (200 ml.) was then added and the mixture was allowed to stir overnight before filtering. The resultant waxy solid was slurried with fresh heptane (300 ml) at room temperature and filtered to afford the crude ester as an off white solid in 40% yield (3.4g). The analytically pure ester was obtained as a white solid after recrystallization from hot ethanol. The analytical data are included in Table 4, and its infrared spectrum is reproduced in Figure 22.

2,4-Dichloro-6-n-butoxy-1,5-naphthyridine (NI-68)

Previously characterized 6-n-butoxy-4-chloro-1,5-naphthyridine-1-N-oxide (10.0g, 39.6 mmole, NI-44) was slowly added as a solid into phosphorous oxychloride (150 ml.) at room temperature. A slight exotherm to 37° was noted during this addition. The mixture was then slowly heated to reflux and maintained at that temperature for a total of six hours. After cooling to room temperature, the excess phosphorous oxychloride was removed via vacuum distillation. The residue was then cautiously hydrolyzed by the dropwise addition of water (40 ml.) with efficient stirring. The resultant slurry was brought to a pH of 9-10 with concentrated ammonium hydroxide. Additional water (ca., 50 ml.) was added and the suspension was filtered to afford the crude product as a white solid in 98% yield (10.5g). The analytically pure product was obtained as a white solid by recrystallization from heptane and vacuum sublimation at 90° (0.02 mm). The analytical data are included in Table 5, and its proton spectrum is reproduced in Figure 28.

6-n-Butoxy-2-chloro-4-methoxy-1,5-naphthyridine (NI-69)

Preformed 6-n-butoxy-2,4-dichloro-1,5-naphthyridine (15.0g, 55.3 mmole, NI-68) was added into a solution of sodium methoxide (11.9g of a 25% methanolic solution, one mole-eq.) in 300 ml. of methanol at 25°. The white suspension was slowly heated to reflux and maintained at that temperature for five hours. The solvent was then removed to afford an off white solid. The solid was triturated with 400 ml. of boiling heptane and filtered while hot to separate the insoluble sodium chloride (2.6g, 80%). The filtrate was then heated to boiling, treated with magnesium sulfate, filtered, and allowed to stand at room temperature for two days. The analytically pure title compound separated from solution and was isolated as colorless needles (0.90g, m.pt. 103-105). An additional crop of this material was isolated after cooling the heptane filtrate to 0° for four hours (3.90g). The overall yield of the pure 6-n-butoxy-2-chloro-4-methoxy-1,5-naphthyridine as isolated via this procedure was 32% (4.80g). We have also now determined that the material balance of this reaction consisted mostly of the retro-isomer, 4-chloro-2-methoxy-6-n-butoxy-1,5-naphthyridine, contaminated with a small amount of unreacted starting material. The analytical data for NI-69 are included in Table 6, and its proton spectrum is reproduced in Figure 37. In addition, the proton spectrum for the impure retroisomer (from the concentrated filtrates) is reproduced in Figure 36.

2-Methoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (NI-70)

With only minor changes in the work-up procedure, the title product was prepared as reported by McCaustland and Cheng (2). Accordingly, a mixture of our previously characterized 4-chloro-2-methoxy-1,5-naphthyridine (3.0g, 15.0 mmole, NI-16), potassium carbonate (2.1g, 15.0 mmole), and 25 ml. of 2-amino-5-diethylaminopentane was heated to 140° for eighteen hours. Very little color change had occurred after this treatment, and the yellow suspension was cooled at room temperature. At this point, 50 ml. of 5 N sodium hydroxide was added with stirring and the two phase system was extracted twice with 75 ml. of ether. The ether phase was dried over magnesium sulfate and both the ether and excess diamine was removed under a strong nitrogen purge for two days. The residual yellow-amber gum was then subjected to molecular distillation. A small amount (ca., 0.5g) of unreacted NI-16 sublimed onto the cold finger at 80-120° (0.06 mm). The title product was then quickly collected in 74% yield (3.5g, 135-150°/0.06 mm) as a pale yellow, almost colorless oil. The analytical data are included in Table 8, and its proton spectrum is reproduced in Figure 53.

4,6-Dichloro-1,5-naphthyridine-
1-N-oxide (NI-71)

A solution of m-chloroperoxybenzoic acid (3.05 g, 15.0 mmole, 1,5 mole-eq. of 85% pure material) in 150 ml. of chloroform was added dropwise at 25° into a colorless solution of our previously characterized 4,6-dichloro-1,5-naphthyridine (2.0 g, 10.0 mmole, NI-23) in 100 ml. of chloroform. After stirring at 25° for three days, the yellow chloroform solution was transferred to a separatory funnel and washed four times with aqueous potassium carbonate (25 g in 300 ml. of water). The aqueous phase was discarded, and the solvent removed via a nitrogen stream to afford the crude product as a yellow solid. This solid was heated to boiling with 300 ml. of heptane and chloroform was added (ca., 80 ml.) until a clear yellow solution was obtained. This solution was treated with magnesium sulfate and filtered. A yellow precipitate separated from the filtrate after cooling to room temperature. After filtration, the title product was isolated as a yellow solid in 74% yield (1.60 g, m. pt. 203-205°). The analytical data are included in Table 5 and its proton spectrum is reproduced in Figure 26.

6-n-Butoxy-4-chloro-2-methoxy-1,5-
naphthyridine (NI-72)

Preformed 6-n-butoxy-2,4-dichloro-1,5-naphthyridine (20.0 g, 73.7 mmole, NI-68) was quickly added into a solution of one mole-equivalent of sodium methoxide (15.8 g of a 25% solution in methanol) in 400 ml. of methanol at 25°. This suspension was then heated to reflux for a total of twenty-four hours. Solvent was then removed from the resultant pale amber solution to afford a white solid. This solid was extracted with 500 ml. of boiling heptane and filtered while hot to afford a quantitative yield of sodium chloride (4.4 g). The colorless filtrate was concentrated to almost four-fifths of its original volume, and was kept at 0° for five hours. The resultant suspension was filtered to afford a white solid. This solid proved to be our previously characterized 6-n-butoxy-2-chloro-4-methoxy-1,5-naphthyridine (8.4 g, 43%, NI-69). The filtrate was then concentrated to 100 ml., cooled to 0° overnight and filtered to afford an additional crop of NI-69. Solvent was then removed from the filtrate, and the resultant semi-solid was triturated with ten ml. of heptane. After filtering a small quantity of white solid, solvent was removed from the heptane filtrate to afford a colorless oil (5.2). This oil was subjected to molecular distillation, and the title product was obtained as a low melting, colorless oil in 20% yield (4.0 g, 105-110°/0.02 mm). A proton spectrum of this oil (Figure 36) revealed the presence of trace amounts of both the retroisomer (NI-69), and unreacted starting material (NI-68). This oil did, however, analyze correctly for the structure as formulated (Table 6).

4.5 Naphthyridine Targets (NT-20 through NT-23)

4,6-Dimethoxy-2-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine di- β -resorcyate hemi-hydrate (NT-20)

A mixture of 2-chloro-4,6-dimethoxy-1,5-naphthyridine (3.0g, 13.3 mmole, NI-42), 2-amino-5-diethylaminopentane (20.0g, 126 mmole), and one mole-equivalent of potassium carbonate (1.84g) was heated at 170° for eighteen hours. After cooling to room temperature, a brown liquid phase was observed along with a considerable quantity of tan solid which adhered to the walls of the flask. A five normal, aqueous solution of sodium hydroxide (50 ml.) was then added with efficient stirring. After transferring to a separatory funnel, the two phase system was extracted three times with 100 ml. of ether. This extraction was complicated by the presence of a flocculant solid (starting material by I.R.) near the ether-water interface. The combined ether layers were then dried over magnesium sulfate and the solvent was removed under a nitrogen purge to afford a dark brown liquid. This liquid was subjected to molecular distillation. Excess diamine was first removed over the range of 35-100° (0.08 mm.). A yellowish semi-solid (ca., 0.5g) then quickly sublimed onto the cold finger at 110-120° (0.08 mm). This solid had an infrared spectrum identical to the 2-chloro-4,6-dimethoxy-1,5-naphthyridine starting material. A yellowish oil was then collected over the range of 145-165° (0.08 mm). A sample of this free base (1.40g, 30% yield) quickly darkened upon exposure to air. The di- β -resorcyate was therefore immediately prepared by the dropwise addition of β -resorcylic acid (1.34g, 8.44 mmole of 97% purity, 2.5 mole-eq.) in 50 ml. of ether into the pale amber solution of the free base (1.17g, 3.38 mmole) in 200 ml. of ether at room temperature. An off-white suspension formed immediately which was stirred at room temperature for an additional two hours. Filtration under a nitrogen atmosphere afforded the title product as an off-white solid in 68% yield (1.50g). This salt proved to be hygroscopic. The analytical data are included in Table 7, and its infrared spectrum is reproduced in Figure 42.

4-Methoxy-6-(2,2,2-trifluoroethoxy)-2-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine di- β -resorcyate (NT-21)

Analytically pure 2-chloro-4-methoxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (3.0g, 10.3 mmole, NI-46), 2-amino-5-diethylaminopentane (20.0g), and a catalytic quantity of copper-bronze (0.5g) were mixed at room temperature and then slowly warmed to 170°. After eighteen hours, the dark brown reaction mixture was cooled to room temperature before adding 50 ml. of 5N sodium hydroxide with vigorous stirring. The mixture was extracted several times with ether until the ether extracts were colorless. The ether extracts were combined, dried over magnesium sulfate,

and the solvent removed to afford a viscous brown oil. This oil was then subjected to molecular distillation. After the removal of excess diamine and several forecuts (25-165°/0.04 mm), the free base distilled as a light amber oil and was isolated in low yield (0.8g, 19%, 165-180°/0.04 mm). The free base (0.75g, 1.81 mmole) was dissolved in 75 ml. of ether and a solution of 2,4-dihydroxybenzoic acid (0.72g of 97% purity, 4.54 mmole) in 25 ml. of ether was added dropwise at room temperature. A suspension formed immediately which was stirred for two hours before filtration under a nitrogen atmosphere. The resultant off-white powder was then dried at 70° (0.10 mm) to afford analytically pure product in 58% yield (0.80g). The analytical data are included in Table 7, and the infrared spectrum is reproduced in Figure 43.

2-Methoxy-6-methyl-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (Free Base)

Our previously characterized 4-chloro-2-methoxy-6-methyl-1,5-naphthyridine (2.00g, 9.56 mmole, NI-52) was slowly added to an excess of 2-amino-5-diethylaminopentane (20.0g) at room temperature. A catalytic quantity of copper-bronze (0.5g) was then added, and the mixture was slowly heated to 140° with the aid of an external oil bath. After two hours, an infrared scan of the mixture disclosed that little, if any, reaction had occurred. The mixture was then raised to 165°, and finally 180°, and maintained at the latter temperature overnight. The cloudy brown suspension was cooled to room temperature, and 50 ml. of 5N sodium hydroxide was added with vigorous stirring. The two phase system was then extracted four times with 150 ml. of ether. The dark brown ether phases were combined, treated with magnesium sulfate and charcoal, and the solvent removed under a nitrogen purge. The residual dark brown liquid was then subjected to a slow, controlled molecular distillation. Excess diamine was first removed at 25-100° (bath temperature)/0.05 mm. A small amount of distillate (0.55g) was then collected as a yellow liquid at 100-145° (0.05 mm). The title product was then isolated in 51% yield (1.60g) as a viscous, amber oil over the range 145-170° (0.05 mm). The analytical data are included in Table 7, and its proton spectrum is reproduced in Figure 39.

2-Methoxy-6-methyl-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine di-β-resorcylate (NT-22)

Preformed 2-methoxy-6-methyl-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (1.10g, 3.33 mmole, for preparation, see above) was dissolved in about 100 ml. of ether at room temperature. A solution of 2,4-dihydroxybenzoic acid (1.32g of 97% purity, 8.34 mmole, 2.5 mole-eq.) in 50 ml. of ether was then added dropwise with stirring. A white suspension formed immediately which was stirred for two hours at room temperature. The suspension was then filtered under a nitrogen blanket, and the crude product was repeatedly washed with ether. The title product was thereby obtained as an off-white solid in 75% yield (1.60g) after drying at 50° (0.10 mm). The analytical data are included in Table 7, and its infrared spectrum is reproduced in Figure 40.

4,6-Dimethoxy-2-(5-isopropylaminopentylamino)-
1,5-naphthyridine di- β -resorcyate hemi-hydrate (NT-23)

A mixture of 2-chloro-4,6-dimethoxy-1,5-naphthyridine (3.0g, 13.3 mmole, NI-42), 5-isopropylaminopentylamine (15.0g, 104 mmole) and one mole-equivalent of potassium carbonate (1.84g) was slowly heated to 165° and maintained at that temperature for eighteen hours. The dark brown mixture was then mixed with 50 ml. of 5N sodium hydroxide. The crude mixture placed in a separatory funnel and extracted three times with ether (100 ml.). A brown oil remained at the ether-water interface after the end of the second extraction. This oil was taken up into the last ether extract by the addition of 50 ml. of tetrahydrofuran. The organic layers were combined, dried over magnesium sulfate, and the solvent was removed to afford a dark brown liquid. This liquid was then subjected to molecular distillation. Excess diamine was first removed at 35-100° (0.05 mm). The free base was then collected as a yellow oil in 43% yield (1.90g) over the range 155-175° (0.05 mm). The di- β -resorcyate salt was then prepared by the dropwise addition of a solution of β -resorcylic acid (2.09g, 13.2 mmole of 97% purity) in 50 ml. of ether into the yellow-amber solution of the free base (1.75g, 5.27 mmole) in 200 ml. of ether at room temperature. A suspension immediately formed which was stirred for two hours before filtration under a nitrogen atmosphere. After washing several times with ether and drying under reduced pressure, the title product was isolated as an off-white solid in 68% yield (2.3g). The analytical data for this moderately hygroscopic salt is included in Table 7, and its infrared spectrum is reproduced in Figure 44.

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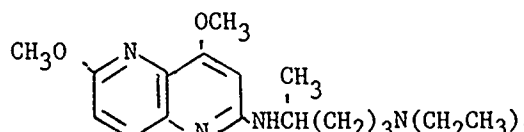
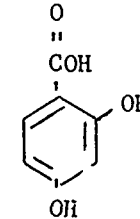
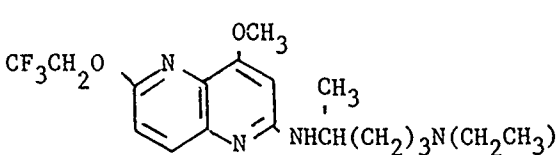
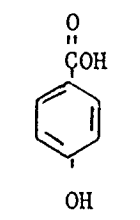
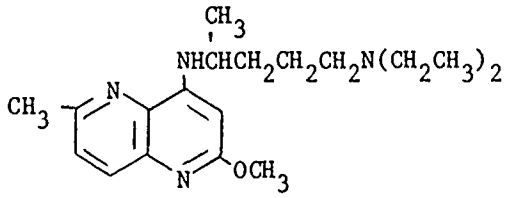
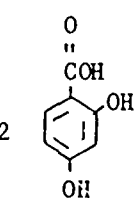
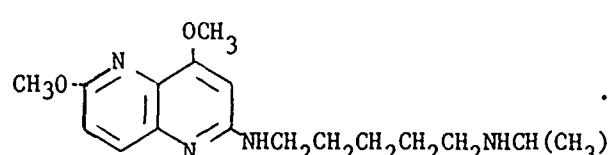
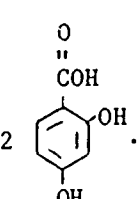
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6. APPENDICES

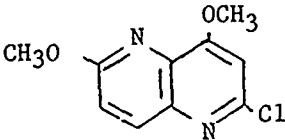
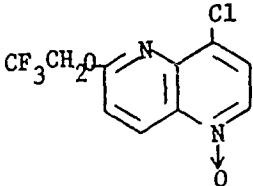
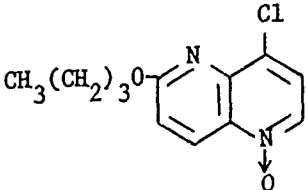
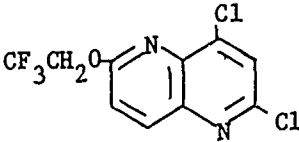
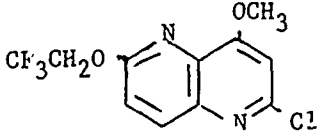
6.1 Numerical Listing of Compounds Submitted

Below are listed the chemical structures and our code designation for each of the compounds which have been submitted for biologic testing this year. Also, all Walter Reed bottle numbers which were available at the time this report was written are included in parentheses directly under our code designation.

Naphthyridine Targets (NT-20 through NT-23)

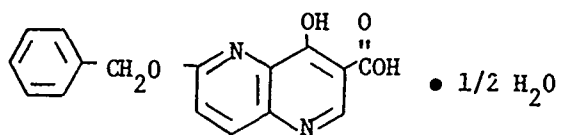
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	. 2 	NT-21 (BE 17295)
	. 2 	NT-22 (BE 67286)
	. 2  .1/2 H ₂ O	NT-23 (BE 67295)

Naphthyridine Intermediates (NI-42 through NI-72)

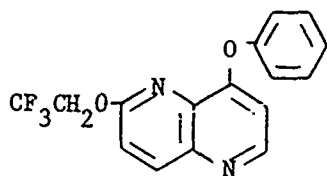
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	NI-43 (BE 17142)
	NI-44 (BE 17151)
	NI-45 (BE 17160)
	NI-46 (BE 17179)

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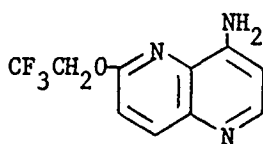
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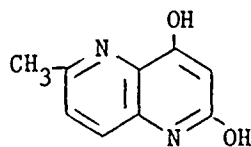
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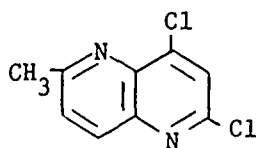
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NI-49
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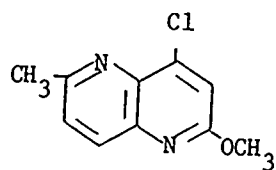
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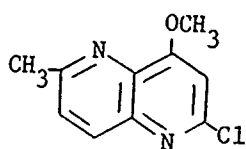
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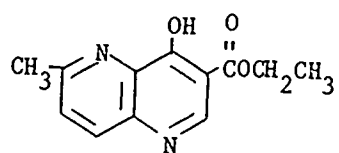
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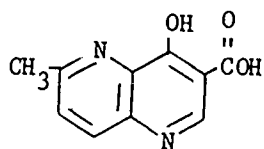
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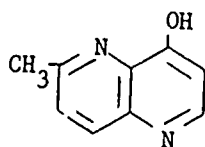
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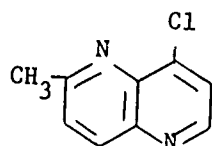
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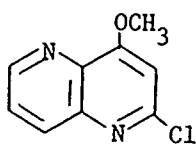
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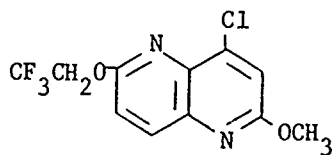
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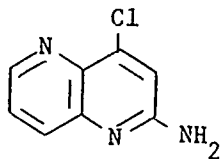
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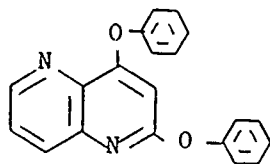
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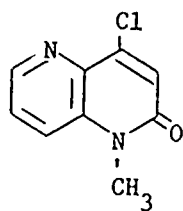
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NI-60
(BE 43955)



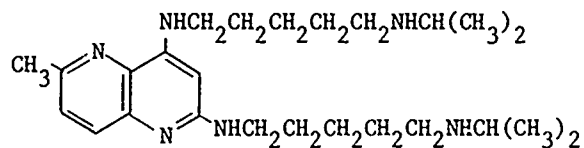
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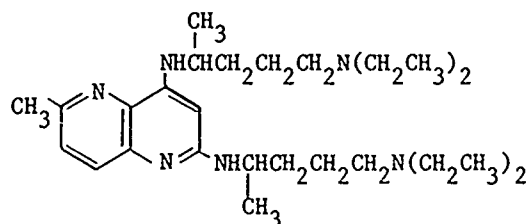
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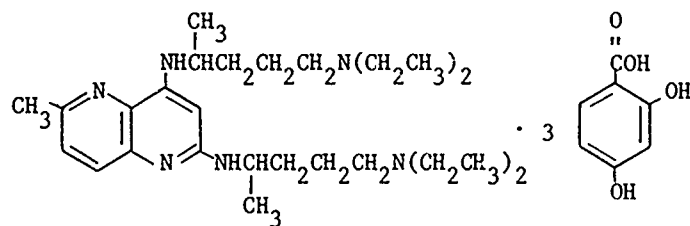
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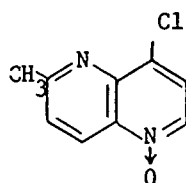
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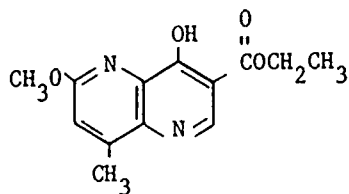
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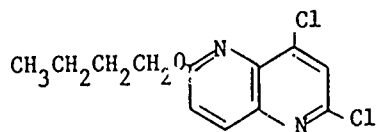
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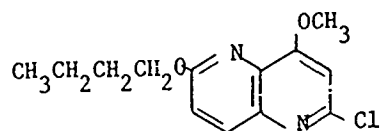
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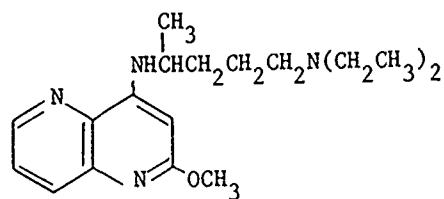
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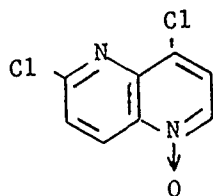
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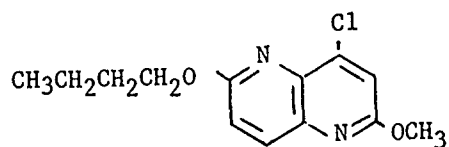
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NI-70
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NI-71

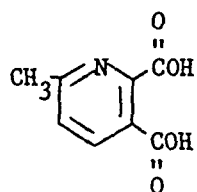


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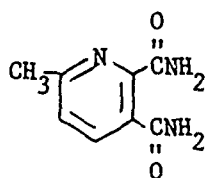
Naphthyridine Precursors (NP-44 through NP-69)

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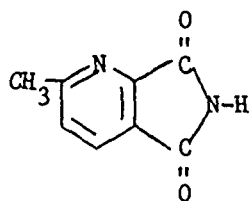
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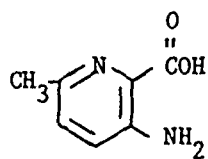
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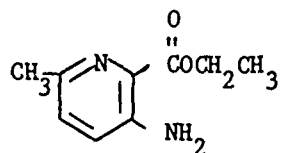
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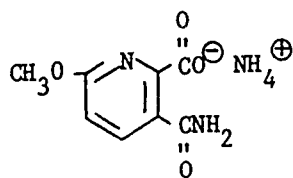
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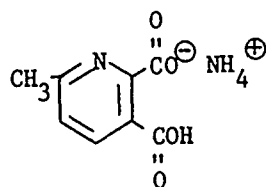
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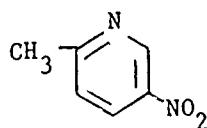
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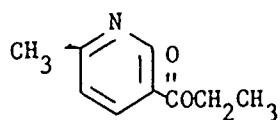
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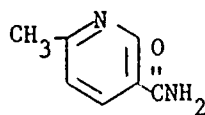
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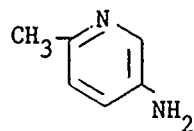
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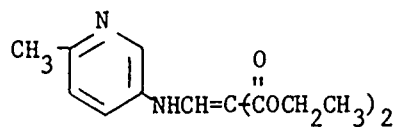
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Structure

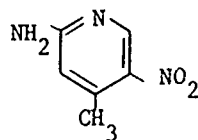
Code Number



NP-54
(BE 44014)



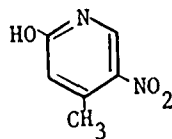
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(BE 44023)



NP-56
(BE 57413)



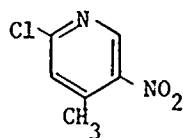
NP-57
(BE 57422)



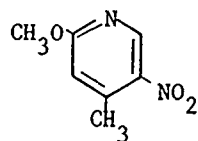
NP-58
(BE 57431)

Structure

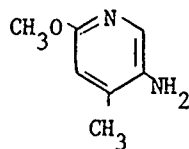
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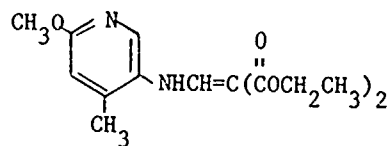
NP-59
(BE 57440)



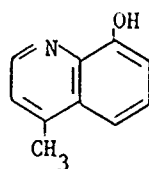
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(BE 57459)



NP-61
(BE 57468)



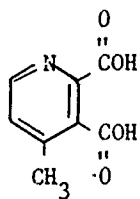
NP-62
(BE 57477)



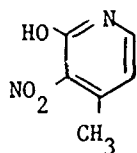
NP-63
(BE 57486)

Structure

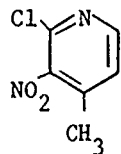
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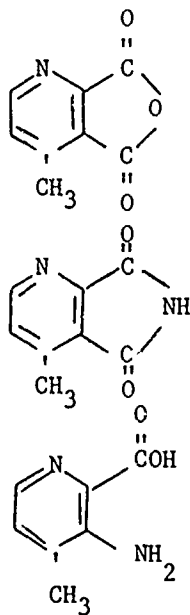
NP-64
(BE 57495)



NP-65
(BE 57502)



NP-66
(BE 57511)



NP-67

NP-68

NP-69

6.2 Biologic Activity Data

Test results for the prophylactic screen have been obtained for most of the target drugs which have been submitted to WRAIR. In general, no significant prophylactic activity has been observed in the Rhesus monkey in the lower dosage range (1.0 mg/kg). However, one target compound, 2-hydroxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (NT-7), has proven to be curative at a dosage level of 10.0 mg/kg.

While biologic testing data are not yet complete in the therapeutic screen, we have included below a summary of the activity data received to date for the target structures submitted to WRAIR. In the following tabulation, the activity data (T-C) are expressed in days and represent the lifetime extension of treated mice at a given dosage level (mg/kg) as compared to controls. The mean survival time of the controls is 6.1 days and a compound is considered "active" if its T-C exceeds 6.1 days. Any deaths which occur in the treated mice from 2 to 5 days after the drug administration are attributed to drug toxicity. The number of these "toxic deaths" at any given dosage level are included in parenthesis. Also, unless otherwise noted, five female mice injected with *Plasmodium berghei* KBG 173 have been used at each dosage level.

Compound		Activity (T-C)						
Code No.	WRAIR No.	10 mg	20	40	80	160	320	640
NT-2	BD 26413	0.2	0.2	1.2	2.8	5.2	9.2	
NT-4	BD 54711		0.1		0.3		0.9(2)	
NT-5	BD 54720			0.1		0.1		0.1
NT-6	BD 54739			0.1		0.1		0.3
NT-8	BD 54757	0.3	0.3	2.9	3.7	5.9	7.9(2)	
NT-9	BD 54766		0.1	0.5	2.1	4.1	6.9	8.9
NT-10	BD 54775			0.1		0.1		0.3
NT-13	BE 10983		0.5	0.7	1.7	3.7	4.5	0.0(5)
NT-14	BE 10992			0.3		0.0(5)		0.0(5)
NT-15	BE 11006	0.1	0.3	0.3	0.5	2.5	5.3	
NT-17	BE 11024			0.3		0.4(1)		0.0(5)
NT-19	BE 13500			0.3		0.5		0.0(5)
NT-20	BE 17286			0.3		0.5		0.0(5)
NT-21	BE 17295			0.3		0.7		1.1

In addition, NP-18 through NP-50 and NI-17 through NI-49 (excluding NI-26 and NI-33) have also been tested in the therapeutic screen at dosage levels of 40, 160 and 640 mg/kg. None of these precursors and intermediates exhibited a T-C in excess of 1.0 day at any dosage level.

6.3 Program Organization and Personnel

This program was conducted in the Government Research Laboratory of Exxon Research and Engineering Company. The principal investigator for this project was Dr. John F. Pilot. During the second year of research on this program, Dr. Pilot was assisted by Mr. Nelson C. Edwards. Dr. Daniel Grafstein, Manager of the Applied Science Section, has been responsible for the administrative aspects of this program.

6.4 Distribution Statement

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