THE SYNTHESIS OF ANALOGS OF CAMPTOTHECIN

DANIEL LEE COMINS
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THE SYNTHESIS OF
ANALOGS OF CAMPTOTHECIN

By

DANIEL L. COMINS

B.A., SUNY at Potsdam, 1972

A THESIS

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MY PARENTS
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ABSTRACT

THE SYNTHESIS OF
ANALOGS OF CAMPTOTHECIN

By

DANIEL L. COMINS

An improved synthesis of a 2-chloro D and E ring analog (10) of Camptothecin has been achieved starting from 3,4-lutidine. The bromination of 1-alkyl-3-methyl-2-pyridines with N-bromosuccinimide was studied as a possible synthetic step in a Camptothecin synthesis. By a proper choice of reaction conditions selectivity could be controlled to give either ring or side chain bromination. A preparation of 2-aryl-4,5-dimethylpyridines was accomplished via a regioselective arylation of 3,4-lutidine. The addition of p-chlorophenylmagnesium bromide to the 1-phenoxy carbonyl salt of 3,4-lutidine followed by aromatization of the intermediate 1,2-dihydropyridine gave 2-p-chlorophenyl-4,5-dimethylpyridine (31) in good yield. Compound 31 was used in the synthesis of a 6-aryl D and E ring analog (37) of Camptothecin.

D and E ring analog 50 is a proposed intermediate for the total synthesis of Camptothecin. Preparation of 1-(3'-bromomethyl-2'-quinolyl)-succinimide (71) and coupling
of 71 with 50 gave an A, B, D and E ring analog (72). The synthesis of 72, a tetracyclic intermediate which requires only the formation of a single bond creating the C-ring of Camptothecin, constitutes a novel approach to the total synthesis of this alkaloid.
SECTION I

INTRODUCTION

Since its isolation and characterization by Wall and co-workers\(^1\) in 1966, the pentacyclic alkaloid camptothecin (\(\text{I}\)) has received considerable attention. Promising anti-leukemic and antitumor properties and the limited availability of the natural material inspired synthetic organic chemists in several laboratories around the world to develop synthetic routes to camptothecin.\(^2\)

Unfortunately, the toxic effects and lack of activity against gastrointestinal cancer showed \(\text{I}\) to be ineffective as a chemotherapeutic agent.\(^3\) The effectiveness of camptothecin against leukemia in experimental animals and its remarkable effect in the inhibition of macromolecular synthesis\(^4\) has caused continued interest in the alkaloid, its analogs, and the structural features associated with this activity.
Although the mode of action of camptothecin has not been elucidated, it has been suggested that the planar molecule could initiate its action by intercalating into the chain of DNA. To help elucidate the mode of action, structure-activity relationships need to be determined. Some information concerning the relationship between structure and activity is available. Previous studies had indicated that the α-hydroxy lactone functionality present in the E ring of 1 was an absolute requirement for antitumor activity and that the D and E rings were a necessary but not sufficient requirement for activity. A recent report confirmed that the α-hydroxy lactone functionality was an absolute requirement for the antitumor activity of camptothecin; however, an analog 2 was prepared which lacked the lactone moiety and retained an activity comparable to dl-camptothecin. This suggested, with regard to structure-activity relationship, that the hydroxy group at C-20 is more significant than the lactone moiety. Danishefsky and co-workers synthesized and tested the C, D and E ring analog 3 and found no activity. Sugasawa and co-workers prepared 4 and reported that it also showed no activity. These results and information obtained from the synthesis and testing of the A, B, D, and E ring analog 5, which was prepared in this laboratory, suggest that a planar system with a C-2 and C-3 bond and/or "the basicity at N-1" is needed for activity.
To test the planarity hypothesis, approaches to the synthesis of analogs of the type 6 and 7 were investigated. Analogs of the type 6 would have orbital overlap of the two aromatic systems which would increase the barrier to rotation about the C-2 - C-3 bond to more than 5.0 kcal/mol and stabilize the planar conformation about that bond. This would provide a planar system which hopefully would give activity in the cancer screen.

The proposed route for the preparation of analogs of the type 6 and 7 required 2-aryl-4,5-disubstituted pyridines. Since no convenient method for their preparation was available, a synthetic route was developed. A study was done on regioselective nucleophilic additions of aryl Grignard reagents to various 1-alkoxycarbonyl salts of 3,4-lutidine. When the 1-phenoxycarbonyl salt of 3,4-lutidine was treated with aryl Grignard reagents, regioselective addition to the less hindered α position occurred. Aromatization of the intermediate 1,2-dihydropyridines gave 2-aryl-4,5-dimethylpyridines as the only or major product. While this work was in progress a second route to 2-aryl-4,5-disubstituted pyridines was developed in these laboratories.

The synthesis, and approaches to the synthesis, of analogs of the type 6 and 7 are discussed in this thesis. An approach to a short and efficient synthesis of camptothecin is also discussed. The proposed synthetic routes to camptothecin are illustrated in Scheme I. The C-ring
SCHEME I

\[ \text{Reactions and chemical structures} \]

1. Reaction with \( X = \text{Br} \) and \( C_2H_5 \text{OH} \)

2. Reaction with \( X = \text{NH}_2 \) and \( C_2H_5 \text{OH} \)

3. Reaction with \( X = \text{Br} \) and \( C_2H_5 \text{OH} \)

4. Reaction with \( X = \text{NH}_2 \) and \( C_2H_5 \text{OH} \)

5. Reaction with \( X = \text{Br} \) and \( C_2H_5 \text{OH} \)

6. Reaction with \( X = \text{NH}_2 \) and \( C_2H_5 \text{OH} \)
was to be formed last through the C-5 - N-4 bond (route A) or via a Pschorr ring closure through the C-2 - C-3 bond (route B).
SECTION II

RESULTS AND DISCUSSION

A. An Improved Synthesis of the 2-Chloro-D- and E-Rings of Camptothecin

The total synthesis of a 2-chloro-D- and E-ring analog (10) was accomplished in this laboratory.\textsuperscript{11} It involved the nine-step sequence illustrated in Scheme II. The synthetic route was very lengthy and the overall yield was about 5%. This made it very difficult to obtain large quantities of \textsuperscript{10} for further study. In order to shorten the synthetic sequence and improve the overall yield, an investigation into an alternative synthesis of intermediate \textsuperscript{9} was initiated.

Meyers and co-workers prepared ester \textsuperscript{13} in good yield by treatment of 3-bromo-4-methylpyridine (12) with lithium diisopropylamide (LDA) in THF followed by addition of diethyl carbonate.\textsuperscript{12} If similar results could be obtained with 3,4-lutidine in place of \textsuperscript{12}, a short route to the intermediate \textsuperscript{9} might be accomplished. Lateral metalation of 3-methylpyridines with strong bases has been reported\textsuperscript{13}; however, this was not expected to be a competing reaction as the 4-methyl protons are considerably more acidic due to resonance stabilization of the resulting anion (see Scheme III).
SCHEME III

12

2LDA

13

14

CH$_2$CO$_2$C$_2$H$_5$

15

C$_2$H$_5$I

16

17
Treatment of 3,4-lutidine with two equivalents of LDA in THF followed by the addition of diethyl carbonate gave anion \( 14 \) in situ. Addition of iodoethane completed the "one pot" synthesis of \( 2-(3'-\text{methyl}-4'-\text{pyridyl})\)-butyrate (15) in 88% yield (Scheme III).

An oxidation of 15 was effected by treatment with potassium t-butoxide in THF at -40° followed by exposure to an oxygen stream.\(^{12}\) This gave the hydroperoxide (16) in 83% yield. Reduction of the hydroperoxide moiety with potassium iodide in methanol-acetic acid was found to be a convenient and efficient method to prepare intermediate 17 in high yield. The overall yield of 17 from 3,4-lutidine was 67%. Previously, this intermediate had been prepared from \( \beta \)-picoline-N-oxide in four steps with an overall yield of about 26%.\(^{11,14}\) With a convenient synthesis of 17, 2-chloro-D- and E-rings (10) could be prepared in multigram quantities.

Two analogs (11) and (5) of camptothecin have been prepared in this laboratory by formation of quaternary salts of 10 followed by pyridone formation\(^{15}\) (see Scheme II). However, due to the weak nucleophilicity of 10, quaternary salt formation was very difficult and efforts toward the preparation of additional analogs by this route were abandoned.
B. Study of an Approach to the C-Ring Cyclization of a Model Compound

One of the routes to the synthesis of Camptothecin proposed for study in this thesis involved a ring closure through the C-2 – C-3 bond (Scheme I, route B). In order to evaluate the feasibility of this route, the reactions of model systems were studied.

Kane had previously prepared the pyridyl-quinoline (19) in this laboratory via the Pfitszinger reaction (Scheme IV). Benzylic bromination of the 3-methyl substituent and intramolecular cyclization should have produced 20. However, when 19 was treated with NBS a perbromide or a hydrobromide apparently formed with the basic nitrogen atom of the pyridine ring and methyl bromination was prevented. To circumvent this problem, he attempted the synthesis of 2-chloro-pyridyl-quinoline (23). The 2-chloro substituent would decrease the basicity of the nitrogen atom and should allow benzylic bromination to proceed. Attempted decarboxylation of 22 did not give 23, probably due to decomposition under the reaction conditions, and this approach was abandoned at this point.

Compounds of the type 23 seemed logical models for cyclization studies and the investigation into their synthesis was continued. Since a 2-chloro substituent appeared to render the quinolinic acid 22 unstable to decarboxylation conditions, a quinolinic acid with a 2-oxygen substituent on the pyridine ring was proposed. The 2-oxygen substituent
SCHEME IV

18 + \( \text{C}_{2}\text{H}_{5}\text{CO}_2\text{H} \) \( \rightarrow \) \( \text{C}_{2}\text{H}_{5}\text{CO}_2\text{H} \) + \( \text{C}_{2}\text{H}_{5}\text{CO}_2\text{H} \) 

19 \( \rightarrow \) \( \text{N}^+ \text{Br}^- \)

21 + 18 \( \rightarrow \) \( \text{C}_{2}\text{H}_{5}\text{CO}_2\text{H} \) 

21 \( \times \)
would decrease the basicity of the pyridine nitrogen atom and hopefully allow the NBS reaction to proceed. It should also stabilize the compound to decarboxylation conditions and would provide a model compound with a good representation of the A, B and D rings of Camptothecin. Pyridyl quinoline 28, with an α-methoxy group on the pyridine ring, was chosen as the target model compound (Scheme V).

The ketal 24 was prepared in good yield from 6-chloro-2-propionylpyridine (21). At this point, the synthetic plan called for a displacement of the α-chloro substituent with methoxide ion. The usual method of displacement is to heat the chloropyridine, methoxide ion, and methanol in a sealed tube at greater than 100°. It was desirable to find a milder and more convenient method of substitution. Alkoxides have been reported to be more powerful nucleophiles when DMSO was used as the solvent. Schmid and Wolkoff prepared several 4-alkoxy pyridines from 4-chloropyridine and various sodium alkoxides in DMSO. Treatment of 24 with sodium methoxide in DMSO at 100° gave 25 in 68% yield.

The ketal protecting group was removed with aqueous oxalic acid to give ketone 26 in 86% yield. The reaction of 26 with isatin (18) in dilute potassium hydroxide gave an 89% yield of the quinolinic acid 27. As predicted, 27 was stable to decarboxylation conditions and pyridyl-quinoline 28 was obtained in 67% yield.
SCHEME V

21 \[\xrightarrow{\text{C}_{2}H_{5}}\] 24 \[\xrightarrow{\text{C}_{2}H_{5}}\] 25

26 \[+18\] \[\xrightarrow{\text{CO}_{2}H}\] 27

\[\xrightarrow{\ast}\] 28 \[\xrightarrow{\text{OCH}_{3}}\] 29

C_{2}H_{5} N\text{Cl} C_{2}H_{5} N OCH_{3}
Unfortunately, when 28 was treated with NBS in refluxing carbon tetrachloride only starting material, 28, and none of the desired product, 29, was identified by nmr in the crude reaction product. Probably the close proximity of the pyridine nitrogen atom deactivates the 3-methyl group on the quinoline ring toward benzylic bromination. Further studies of the cyclization of the model compound 28 were abandoned.

C. Bromination of 1-Alkyl-3-methyl-2-pyridones with N-Bromo-succinimide

With a convenient procedure for the functionalization of the 4-methyl group of 3,4-lutidine available (Section II, A), the possibility of using intermediates of the type 30 for the synthesis of camptothecin analogs was investigated. If 30 were to be a synthetic intermediate, the 3-methyl group had to be susceptible to facile functionalization. A study was made of the bromination of 1-alkyl-3-methyl-2-pyridones with NBS. This work has been published and is shown in Appendix C.
D. Preparation of 2-Aryl-4,5-dimethylpyridines

The failure of N-arylmethyl D- and E-ring analogs to give antitumor activity suggests that the aryl group must be coplanar with the D- and E-rings. Perhaps this would allow intercalation to occur.\(^5\) Compounds such as 6 or 7 (see Section I) should have a low energy conformation in which the aryl group and the D- and E-rings are coplanar to allow resonance interaction. Screening of analogs of this type should give indication of the validity of the intercalation hypothesis.

The proposed route for the preparation of these analogs required a convenient method for the synthesis of 2-aryl-4,5-dimethylpyridines. The addition of organometallic reagents to the pyridine nucleus is a well established route for preparing substituted pyridines; however, the usual orientation of addition to a 3-alkylpyridine is at the 2-position and not at the desired 6-position.\(^21\) The introduction of large steric hindrance at the 1-position of a 3,4-lutidine derivative was anticipated to give regioselective nucleophilic addition at the 6-position. The addition of aryl Grignard reagents to various 1-alkoxycarbonyl salts of 3,4-lutidine was investigated. Regioselective addition was achieved when the 1-phenoxy carbonyl salt of 3,4-lutidine was treated with an aryl Grignard reagent. Aromatization of the intermediate 1,2-dihydropyridines
gave 2-aryl-4,5-dimethylpyridines in moderate yields. This work has been published and is shown in Appendix D.
E. Synthesis of BDE Ring Analogs of Camptothecin

Having developed a convenient method for the preparation of 2-aryl-4,5-dimethylpyridines, an effort was directed toward the elaboration of these simple arylpyridines to provide analogs of Camptothecin (see Scheme VI).

Treatment of 2-(p-chlorophenyl)-4,5-dimethylpyridine (31) with 40% peracetic acid gave the N-oxide (32) in 71% yield. Conversion of the N-oxide (32) to 2-(p-chlorophenyl)-4,5-dimethyl-6-chloropyridine (33) was effected in 63% yield with phosphorus oxychloride. Heating 33 with sodium methoxide in DMSO gave 2-(p-chlorophenyl)-4,5-dimethyl-6-methoxypyridine (34) in 78% yield. At this point the synthetic plan called for functionalization of the methyl group at the 4-position. It was hoped that the method used to convert 3,4-lutidine to ethyl 2-(3'-methyl-4'-pyridyl)-butyrate (15) (Section II,A) would also effect the elaboration of 34. When 34 was treated with two equivalents of LDA followed by the addition of diethyl carbonate and then iodoethane, a 75% yield of 35 was obtained. Benzylic bromination of 35 with N-bromosuccinimide gave 36 in 99% yield. The bromomethyl compound (36) was converted to the lactone (37) via acid hydrolysis (2N H$_2$SO$_4$-DME) in 70% yield.

Analog 37 will be screened for inhibition of nucleic acid synthesis in HeLa cells. Oxidation of 37, by the method previously described (Section II,A), would give the
SCHEME VI

31 $\rightarrow$ CH $\rightarrow$ CH $\rightarrow$ CH

31 $\rightarrow$ Cl 31 $\rightarrow$ Cl 33 32

34 $\rightarrow$ CH $\rightarrow$ OCH $\rightarrow$ Cl 35

34 $\rightarrow$ Cl 36 $\rightarrow$ OCH 37

36 $\rightarrow$ CH $\rightarrow$ OCH 37

36 $\rightarrow$ C2H5 39 $\rightarrow$ C2H5 39 a, R=H
dashed line 39 b, R=OH
α-hydroxy lactone (38). This analog (38) would have the E ring functionalization needed for anticancer activity\(^8\) and will be screened against L1210 leukemia. The synthesis of analog 39, via treatment of 37 or 38 with hydrobromic acid\(^{25}\), is proposed for future work.

With a synthetic route developed for the preparation of B,D and E ring analogs of the type 6, approaches to the synthesis of 7 were investigated. Since ethyl 2-(3'-methyl-4'-pyridyl)-butyrate (15) was so readily available (Section II,A), an attempt was made to arylate regioselectively compound 15 (Scheme VII). Treatment of the ethoxycarbonyl salt of 15 with o-tolylmagnesium bromide, followed by aromatization of the intermediate dihydropyridine with sulfur, gave 40 in 60% yield. The nucleophilic addition was regioselective to greater than 95% and unchanged starting material (15) could be recovered in 29% yield. The high yield of this conversion gave further indication of the rapid reaction of a Grignard reagent with a pyridinium ring, for the pyridinium ring contained a reactive ester function and an acidic hydrogen α to the ester and the pyridine ring. The yield was very satisfactory considering that 3,4-lutidine gave a lower yield (46%)\(^{10}\) in the analogous reaction.

Oxidation of 40 with oxygen and potassium t-butoxide and reduction of the intermediate hydroperoxide with potassium iodide in methanol-acetic acid provided a 93% yield of 41.
In one instance the product was contaminated with a small amount of the corresponding methyl ester, which probably formed via transesterification with the solvent under the reaction conditions. This problem was avoided by using acetic acid as the solvent for the reduction step.26

Treatment of 41 with m-chloroperbenzoic acid in chloroform at room temperature and in the dark for five days, gave an 89% yield of the N-oxide (42). m-Chloroperbenzoic acid is a mild and effective reagent for the preparation of pyridine and arylpyridine N-oxides.27 Conversion of the N-oxide (42) to the 6-chloropyridine (43) was effected in 69% yield with phosphorus oxychloride. Two attempts to brominate the methyl group(s) of 43 with NBS failed and only starting material (43) was recovered. The reason the bromination failed is not clear, for an analogous compound, differing only in that it had no aryl substituent, underwent normal benzylic bromination with NBS.11 The combination of the 2-aryl group and the α-hydroxyester in some way interferes with the benzylic bromination. Plans for further elaboration of compound 43 were abandoned.

While the above work was in progress the analogous series (45)-(49), in which the aryl group is o-methoxy-methylphenyl, was also being examined. The early incorporation of an o-methoxymethyl group on the phenyl ring was designed to circumvent possible problems in functionalization of the o-methyl group at a later stage, for benzylic bromi-
nation with NBS failed with a model compound (28) (Section II, B). Treatment of the phenoxycarbonyl salt of 15 with o-methoxymethylphenylmagnesium iodide followed by aromatization gave a mixture of 45 and 46 in 24% and 12% yields respectively (see Scheme VIII). The lack of regioselectivity in this reaction is surprising since the analogous reaction with o-tolylmagnesium bromide gave nearly exclusive addition at the 6-position of the pyridine ring (Scheme VII).

Oxidation of 45 with oxygen and potassium t-butoxide and reduction of the intermediate hydroperoxide with sodium iodide in acetic acid gave 47 in 73% yield. Treatment of 47 with m-chloroperbenzoic acid gave a 89% yield of the N-oxide (48). When 48 was treated with phosphorous oxychloride, only a low yield of a brown viscous oil was isolated from the reaction mixture. The crude residue was shown to contain two major components by thin layer chromatography. Because of this complication, in conjunction with the problem found with the attempted benzylic bromination of 43, studies on the above synthetic route were terminated.
SCHEME VII

15 \[\xrightarrow{}\] 40

HO

\[\xrightarrow{}\]

\[\xrightarrow{}\] 42

43

\[\xrightarrow{}\]

44
SCHEME VIII

15 →

CO₂C₂H₅

C₂H₅

H

CH₂OCH₃

CH₃

47

CO₂C₂H₅

C₂H₅

H

CH₂OCH₃

CH₃

48

→

46

49

HO

C₂H₅

CO₂C₂H₅

N

H

C₂H₅

CO₂C₂H₅

N

CH₂OCH₃

CH₃

Cl
F. A Short Route to the D and E Rings

In order to investigate the feasibility of the Camptothecin synthesis by forming the C ring last through the C-2 - C-3 bond (Scheme I, route B), a short route to the D and E ring analog (50) or (51) was needed.

Treatment of 10 with sodium ethoxide in refluxing ethanol gave none of the desired 2-ethoxy D and E ring analog\(^\text{14}\); however, the 2-methoxy D and E ring analog (50) was obtained when 10 was treated with sodium methoxide in DMSO (Scheme IX). Even with the recent improvement in the synthesis of 10 (Section II,A), the route was lengthy and the overall yield was low. The major problem with the preparation of 10 was the loss of approximately half of the material in the last step of the synthesis due to the formation of a mixture of isomers.\(^\text{11,14}\) To avoid the step which introduces the mixture of isomers (Scheme II), an approach to the synthesis of 50 from 2-bromo-3,4-dimethylpyridine (53) was investigated.

The preparation of 2-bromo-3,4-dimethylpyridine (53) from 2-amino-3,4-dimethylpyridine (Reilly Tar and Chemical, custom synthesis) had been reported\(^\text{28}\); however, the synthesis of 2-amino-3,4-dimethylpyridine via the amination of 3,4-lutidine with sodium amide had not been fully examined.\(^\text{29}\) Treatment of 3-substituted pyridines with sodium amide gives predominantly the 2-amino-3-substituted pyridine rather than the less hindered 6-isomer.\(^\text{30}\) Amination of 3-picoline gave
a mixture of 2-amino-3-methylpyridine and 2-amino-5-methylpyridine in the ratio of 10.5:1\textsuperscript{31,32} and it was anticipated that the analogous reaction with 3,4-lutidine would give similar results. However, when 3,4-lutidine was treated with sodium amide in dimethylaniline a 40% yield of 52a and 52b was obtained as a white solid in the ratio of 4:1 (Scheme IX). An efficient separation of the two isomers could not be obtained; therefore, the mixture was converted to the bromopyridines with sodium nitrite, hydrobromic acid, and bromine.\textsuperscript{28} When the crude mixture of bromopyridines was dissolved in hexane and cooled, 2-bromo-3,4-dimethylpyridine (53) crystallized from the solution. Large quantities of 53 could be prepared by this method.

Treatment of 53 with sodium methoxide in DMSO gave 2-methoxy-3,4-dimethylpyridine (54) in 87% yield. The reaction of 54 with LDA, diethylcarbonate, and iodoethane, as in the preparation of 15, gave a 71% yield of 55. Oxidation of 55 with potassium t-butoxide and oxygen and reduction of the intermediate hydroperoxide with sodium iodide in acetic acid gave the α-hydroxyester (56) in 90% yield. Benzylic bromination of 56 with NBS gave 57 in quantitative yield. Conversion of 57 to the acetate (58) followed by acid hydrolysis gave the lactone (50) in 60% yield from the bromide (57). When a small sample of 50 was heated with HBr in acetic acid at reflux for three hours, a tan solid was isolated in low yield. The crude product was shown by nmr
SCHEME IX

10 \rightarrow 50 \rightarrow \begin{array}{c}
\text{51 a, } R=H \\
\text{b, } R=\text{Ac}
\end{array}

\begin{array}{c}
\text{52a} \\
\text{52b}
\end{array}

\begin{array}{c}
\text{53} \\
\text{54a} \\
\text{55}
\end{array}

\begin{array}{c}
\text{56} \\
\text{57} \\
\text{58}
\end{array}

58 \rightarrow 50
to contain two major components, pyridone-lactone (5la) and possibly the corresponding acetate (5lb). The structure of 5lb was suggested by a strong signal in the nmr at 2.2 ppm, which is characteristic of the acetate methyl group. The acetate could have been formed via esterification with the solvent under the reaction conditions. Because of this problem, and the low solubility of 51 in most organic solvents, the preparation of the deoxy derivative 60 was investigated (Scheme X).

Benzylic bromination of 55 with NBS gave 59 in quantitative yield. Treatment of 59 with refluxing 48% HBr effected a one step pyridone and lactone formation to give 60 in 61% yield. This represents an efficient four step synthesis of a deoxy D and E ring analog of Camptothecin from 2-bromo-3,4-dimethylpyridine (53) in an overall yield of 38%.

Oxidation of 60 should provide a convenient preparation of D and E ring analog 51a, and investigation of this reaction is proposed for further study.
SCHEME X

55

\[ \text{Scheme Diagram} \]

59

51a

60
G. An Approach to the Synthesis of Camptothecin

The plan of approach for the synthesis of Camptothecin via route B (Scheme I) required the N-alkylation of a D and E ring analog with an appropriately substituted 3-bromomethyl quinoline. Since a convenient preparation of the D and E ring analog \(50\) had been developed (Section II, F), the N-alkylation of \(50\) was investigated.

The reactions of 2-alkoxypyridines with alkylhalides give N-alkyl-2-pyridones.\(^{33}\) To determine whether the 2-methoxy D and E ring analog \((50)\) would react in a similar manner, a series of nmr tube reactions was studied (Scheme XI). The 2-methoxy D and E ring analog \((50)\) (20 mg) and one equivalent of 2-chloro-3-bromomethylquinoline \((61)\) \(^{14}\) were dissolved in approximately one ml of \(d_6\)-DMSO in an nmr tube. The nmr spectrum was determined and the tube was placed in an oven at 110-120\({}^{\circ}\). The tube was removed, cooled, and the spectra were rerun after 2 and 15 hr, respectively. The nmr spectrum taken after 2 hr showed an appearance of a new doublet at approximately 6.6 ppm. This is an indication of the presence of a C-5 hydrogen of a 2-pyridone ring. It was apparent that the anticipated reaction was occurring and was approximately 40% complete after two hours. There seemed to be a secondary reaction however. The singlet for the C-4 hydrogen of the 2-chloroquinoline \((61)\) was shifting upfield faster than the signals for the hydrogens of the pyridine ring.
SCHEME XI

\begin{align*}
&\begin{array}{c}
\text{C}_2\text{H}_5 \\
\text{HO} \\
\text{N} \\
\text{OCH}_3
\end{array} + \\
&\begin{array}{c}
\text{CH}_2\text{Br} \\
\text{Cl}
\end{array} \\
\rightarrow \\
&\begin{array}{c}
\text{N} \\
\text{Cl}
\end{array} \\
\begin{array}{c}
\text{HO} \\
\text{C}_2\text{H}_5
\end{array} + \\
&\begin{array}{c}
\text{N} \\
\text{H}
\end{array}
\begin{array}{c}
\text{O} \\
\text{HO} \\
\text{C}_2\text{H}_5
\end{array}
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{Cl}
\end{array}
\begin{array}{c}
\text{N} \\
\text{O}
\end{array} \\
\rightarrow \\
&\begin{array}{c}
\text{NO}_2 \\
\text{HO} \\
\text{C}_2\text{H}_5
\end{array}
\end{align*}
of 50. The reaction of the 2-chloroquinoline with DMSO to give quinolone formation was suspected and 63 was probably the major product. Harris34 has reported the facile conversion of 4-chloroquinolines to 4-quinolones in DMSO at 100° for 2 hr. The reaction was thought to occur by addition of the nucleophilic oxygen of DMSO followed by elimination of dimethylsulfide to give the quinolone.34

In order to avoid this problem, an analogous nmr tube reaction was run using DMF as the solvent. Pyridone formation did occur as anticipated; however, after 26 hr the reaction was less than 50% complete and signals from small amounts of by-products were beginning to appear in the nmr spectrum. The reaction was repeated using sulfolane as the solvent; however, no pyridone formation was observed after 20 hr.

The reaction of the D and E ring analog (50) and o-nitrobenzylchloride (64) was also studied on an nmr tube scale using d6-DMSO as solvent (Appendix B, Figures 32a, 32b). As anticipated, pyridone formation occurred to give 65 and was approximately 90% complete in 19 hr. This reaction was not contaminated with by-products and appeared to be a practical route for large scale preparation of compounds of this type. Investigation into a preparative scale reaction is proposed for further work.

Effort was now directed toward the synthesis of an appropriately substituted 3-bromomethylquinoline which could be joined to the D and E ring analog (50), by the method
described above, to give a Camptothecin intermediate. Although a 2-chloro-substituent was not compatible with the conditions used in the coupling reaction, a 3-bromomethyl-quinoline with a protected 2-amino group should be stable and provide the proper functionality for elaboration to Camptothecin. The synthesis of 1-(3'-bromomethyl-2'-quinolyl)-succinimide (71) was proposed and investigated (Scheme XII).

Lithioacetonitrile has been prepared and condensed with aldehydes and ketones to give good yields of β-hydroxy-nitriles. If lithiopropionitrile (66) could be prepared, addition of diethylchlorophosphosphate would provide a convenient synthesis of the Horner-Wittig reagent (67) needed for the synthesis of the intermediate 68 in the preparation of 71. Treatment of propionitrile with two equivalents of LDA gave lithiopropionitrile (66) in situ. Addition of diethylchlorophosphate gave, after hydrolysis, a 63% yield of the desired diethyl 1-cyanoethanephosphonate (67). The reaction of 67 with potassium t-butoxide followed by the addition of o-nitrobenzaldehyde gave 2-(o-nitrobenzylidine)propionitrile (68) in 85% yield. A 43% yield of 2-amino-3-methylquinoline (69) was obtained by the treatment of 68 with sodium dithionite in refluxing aqueous methanol. The amino group could be protected as the succinimide (70) in 56% yield. At this point the synthetic plan called for the benzylic bromination of the 3-methyl group. Compound 70 was not soluble in carbon tetrachloride or benzene, so ethylene chloride was
SCHEME XII

\[ \text{CH}_3\text{CH}_2\text{CN} \rightarrow \text{LiCHCN} \rightarrow \text{C}_2\text{H}_5\text{O}-\text{P-CHCN} \]

\[ \text{NO}_2 \text{C} \rightarrow \text{CH}_3 \rightarrow \text{N} \]

\[ \text{CH}_3 \text{CH}_2\text{CN} \rightarrow \text{LiCHCN} \rightarrow \text{C}_2\text{H}_5\text{O}-\text{P-CHCN} \]

\[ \text{NO}_2 \text{C} \rightarrow \text{CH}_3 \rightarrow \text{N} \]

\[ \text{CH}_3 \text{CH}_2\text{CN} \rightarrow \text{LiCHCN} \rightarrow \text{C}_2\text{H}_5\text{O}-\text{P-CHCN} \]

\[ \text{NO}_2 \text{C} \rightarrow \text{CH}_3 \rightarrow \text{N} \]
used as solvent for the NBS reaction. After purification by HPLC, 1-(3'-bromethyl-2'-quinoly1)-succinimide (71) was isolated in 53% yield.

A mixture of the 2-methoxy D and E ring analog (50) (20 mg) and 29 mg of 71 was dissolved in approximately 1 ml of d6-DMSO in an nmr tube. The tube was placed in an oven at 110-120°. After four hours the reaction was virtually complete and 72 was indicated by nmr to be the sole product (Appendix B, Figures 33a, 33b). Compound 72 could be used as an intermediate in the synthesis of Camptothecin as is illustrated in Scheme XIII.

Oxidation of 72 and subsequent hydrolysis of the succinimide protecting group will give the N-oxide (73). A Pschorr ring closure will provide dl-Camptothecin N-oxide (74). Reduction of 74 with hydrogen and palladium on charcoal will conclude the total synthesis of dl-Camptothecin (1).

The synthesis of 72, a tetracyclic intermediate which requires only the formation of a single bond creating the C-ring of Camptothecin, constitutes a novel approach to the total synthesis of this alkaloid. The use of the Pschorr cyclization has not been applied to this synthesis previously but should lead effectively to the key precursor 74. This approach shows the development of a short, practical route to 72 which is a logical intermediate in the synthesis of Camptothecin.
SCHEME XIII

50 + 71 → 72

73 → 74

1
SECTION III

EXPERIMENTAL

General

Melting Points. Melting points were determined with a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected.

Boiling Points. Boiling points were measured at the pressure indicated in parentheses and are uncorrected.

Infrared Spectra. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord prism spectrometer and were calibrated with polystyrene at 1601.4 cm$^{-1}$. All solid samples were recorded as KBr discs while liquid samples were recorded as neat films between sodium chloride plates.

Nuclear Magnetic Resonance Spectra (nmr). Nuclear magnetic resonance spectra were recorded on a JEOL MH 100 Spectrometer and are reported in parts per million ($\delta$) downfield from TMS. Samples recorded in CDCl$_3$ contain 1% TMS as an internal standard, and samples recorded in TFA and d$_6$-DMSO are calibrated with TMS as an external standard. For all new compounds reported, the nmr spectra are reproduced in Appendix B or given in the experimental section for each new compound as follows: nmr (solvent); in ppm (multiplicity, number of hydrogens). The description of multiplicity is s=singlet, d=doublet, q-quartet and m-multiplet.
Elemental Analyses. Elemental analyses were determined at the University of New Hampshire with an F&M Model 185 carbon, hydrogen and nitrogen analyzer.

Materials and Methods. A. Reagents: Diisopropylamine, diethyl carbonate, iodoethane, ethyl chloroformate, isatin, m-chloroperbenzoic acid, o-bromotoluene, o-nitrobenzaldehyde, o-nitrobenzyl chloride, propionitrile, and sodium methoxide were all purchased from Aldrich Chemical Company. Phosphorous oxychloride, NBS, and phenyl chloroformate were purchased from Eastman, while concentrated hydrochloric and hydrobromic acids were purchased from Mallinckrodt. n-Butyllithium, sodium amide, and potassium t-butoxide were purchased from Ventron Corporation. Peroxyacetic acid (40%) was purchased from FMC Corporation and 3,4-lutidine was a generous gift of Reilly Tar and Chemical Company. Sodium dithionite and potassium acetate were purchased from Baker Chemical Co.

B. Solvents: The following solvents were used without further purification: chloroform, drum ether, ethyl acetate, ethanol, methanol, spectra grade carbon tetrachloride, pentane, hexane, and petroleum ether. Benzene and anhydrous ether were stored over sodium wire. Dimethylsulfoxide (DMSO) and methyl ethyl ketone (MEK) were distilled and stored over 4-A molecular sieves. Tetrahydrofuran (THF) was distilled from calcium hydride and lithium aluminum
hydride using triphenylmethane as indicator and stored over 4-A molecular sieves.

C. Yields of the products are reported on the crude material unless stated otherwise, and usually were of sufficient purity to be used in the following synthetic procedure. Infrared spectra were taken on the analytically pure samples, and nmr spectra were recorded on either the crude or purified product.

D. Experimental Methods: Reagents were weighed to the number of significant figures shown and this number was converted to either moles (mol) or millimoles (mmol). Following extraction, the normal procedure was to wash with saturated sodium chloride solution (brine) and dry the organic solution over the drying agent shown. The solution was filtered and the filtrate was then concentrated under reduced pressure on the rotatory evaporator.

E. Preparative Chromatography: Preparative high pressure liquid chromatography (HPLC) was performed on a WATERS ASSOCIATES Prep LC/system 500. Prep-PAK-500/silica cartridges were used with the solvent(s) indicated.
Preparation of 2-Ethyl-2-(6'-chloro-2'-pyridyl)-1,3-dioxolane (24). Ethylene glycol (20 ml), 15.73 g (0.083 mol) of p-toluenesulfonic acid, 9.34 g (0.055 mol) of 6-chloro-2-propionylpyridine, and 150 ml of dry benzene were placed in a 250 ml flask fitted with a Soxhlet extractor charged with 20 g of conditioned Linde 3A molecular sieves and provided with a condenser. The mixture was stirred magnetically and heated under reflux for 3 days. A solution of 13.4 g of sodium methoxide in anhydrous methanol (100 ml) was added slowly to the stirred mixture, 75 ml of 5% NaOH solution and 75 ml of CHCl₃ were added to the residue, and the aqueous layer was extracted with CHCl₃ (2x75 ml). The combined CHCl₃ extracts were washed with brine, dried (K₂CO₃), and concentrated to give 10.81 g of a yellow oil. Distillation of this oil gave 7.1 g (60%) of 2-ethyl-2-(6'-chloro-2'-pyridyl)-1,3-dioxolane (24) as a clear oil, bp 153-160°/14 mm; ir (Appendix A, Figure 2); nmr (Appendix B, Figure 2).

Anal. Calcd for C_{10}H_{12}ClNO₂: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.26; H, 5.77; N, 6.74.

Preparation of 2-Ethyl-2-(6'-methoxy-2'-pyridyl)-1,3-dioxolane (25). A mixture of 10.61 g (49.66 mmol) of 2-ethyl-2-(6'-chloro-2'-pyridyl)-1,3-dioxolane (24) and 8.05 g (0.15 mol) of sodium methoxide in 50 ml of dry DMSO was heated with stirring at 100° in an oil bath for 20 hr under a nitrogen atmosphere. The solution was cooled, poured into 150 ml of water, and extracted with four 50 ml portions of
ether. The ether extracts were washed with brine, dried (K₂CO₃) and concentrated, and the residual liquid was distilled to give 7.1 g (68%) of 25 as a clear oil, bp 66-71°/0.24 mm; ir (Appendix A, Figure 3); nmr (Appendix B, Figure 3).

**Anal.** Calcd for C₁₁H₁₅NO₃: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.29; H, 6.99; N, 6.98.

**Preparation of 6-Methoxy-2-propionylpyridine (26).** A mixture of 5.9 g (28.2 mmol) of 2-ethyl-2-(6'-methoxy-2'-pyridyl)-1,3-dioxolane (25) and 10.67 g (84.6 mmol) of oxalic acid in 100 ml water was heated under reflux for 2 hr. The reaction mixture was cooled, made basic with 10% NaOH solution and extracted with ether. The ether extracts were washed with brine, dried (K₂CO₃), and concentrated, and the residual liquid was distilled to give 3.99 g (86%) of 6-methoxy-2-propionylpyridine (26) as a clear oil, bp 121-124°/15 mm; ir (Appendix A, Figure 4); nmr (Appendix B, Figure 4).

**Anal.** Calcd for C₉H₁₁N₂O₂: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.19; H, 6.74; N, 8.34.

**Preparation of 2-(6'-Methoxy-2'-pyridyl)-3-methyl-quinolinic Acid (27).** To 2.86 g (19.43 mmol) of isatin (18) in 60 ml of 35% KOH solution was added 3.21 g (19.43 mmol) of 6-methoxy-2-propionylpyridine (26). The mixture was heated under reflux for 3 hr, cooled to room temperature and poured into 75 ml water. The solution was made acidic with concentrated HCl. The solid that precipitated was collected.
by filtration, washed with water, and dried to give 5.06 g (89%) of \( \text{27} \), mp 232-233°; ir (Appendix A, Figure 5); nmr (Appendix B, Figure 5). An analytical sample was prepared by two recrystallizations from isopropanol to give \( \text{27} \) as a white solid, mp 234-235°.

Anal. Calcd for \( \text{C}_{17}\text{H}_{14}\text{N}_{2}\text{O}_{3} \): C, 69.38; H, 4.80; N, 9.52. Found: C, 69.28; H, 4.65; N, 9.63.

Preparation of 2-(6'-Methoxy-2'-pyridyl)-3-methyl-quinoline (28). To 1.31 g (4.45 mmol) of 2-(6'-methoxy-2'-pyridyl)-3-methylquinolinic acid (27) was added 1.3 g of copper powder and 25 ml of freshly distilled quinoline. The mixture was heated under reflux for 5 hr. Isopropanol and Norite were added to the mixture and heating was continued for 10 min. The mixture was filtered through Celite. The isopropanol and most of the quinoline were removed by distillation under reduced pressure. The residue was dissolved in 100 ml of ether, was washed with 5% NaOH, water and brine, and was dried \( \text{K}_2\text{CO}_3 \). Evaporation of the solvent gave a brown oil, which was dissolved in 100 ml of \( \text{CHCl}_3 \), treated with Norit, and filtered through a Florisil pad. Concentration of the solution and recrystallization of the residue from hexane gave 0.75 g (67%) of \( \text{28} \) as a white solid, mp 92-93°; ir (Appendix A, Figure 6); nmr (Appendix B, Figure 6).

Attempted Preparation of 2-(6'-methoxy-2'-pyridyl)-3-bromomethylquinoline (29). A mixture of 200 mg (0.80 mmol) of 2-(6'-methoxy-2'-pyridyl)-3-methylquinoline (28), 142 mg (0.80 mmol) of recrystallized NBS, a catalytic amount of dibenzoyl peroxide, and 25 ml of CCl₄ was heated under reflux for 4 hr by means of a 100-watt bulb. The mixture was cooled in an ice bath and filtered. The filter cake was washed with CCl₄, and the filtrate was concentrated under reduced pressure to give 130 mg of a red oil. This oil was shown by nmr to be mainly starting material 28 with the absence of any of the desired product 29.

Preparation of Ethyl 2-(3'-methyl-4'-pyridyl)butyrate (15). A solution of 44.6 g (0.44 m) of diisopropylamine in 300 ml of anhydrous THF was stirred under a positive pressure of nitrogen at -70° (isopropanol-Dry Ice) while 176 ml (0.44 mol) of 2.5 M n-BuLi in hexane was added over 10 min and allowed to stir for 15 min. A solution of 21.42 g (0.2 mol) of 3,4-lutidine in 40 ml of THF was added dropwise over a period of 5 min and stirring was continued for 15 min. Then 35.44 g (0.3 mol) of diethyl carbonate was added dropwise over 5 min. The cooling bath was removed and stirring was continued for 30 min. Ethyl iodide (35.87 g, 0.23 m) was added, and stirring was continued at room temperature for 1.5 hr. The reaction mixture was hydrolyzed with 100 ml of water, and the aqueous layer was extracted with 100 ml of ether. The organic layers were combined, washed with water
brine, dried ($K_2CO_3$), and concentrated under reduced pressure. The residual liquid was distilled to give 36.6 g (88%) of 15 as a clear oil, bp 84-94°/0.18 mm; ir$^{38}$; nmr$^{39}$.

**Anal. Calcd for $C_{12}H_{17}NO_2$:** C, 69.53; H, 8.28; N, 6.76. Found: C, 69.37; H, 8.21; N, 6.72.

**Preparation of Ethyl 2-Hydroperoxy-2-(3'-methyl-4'-pyridyl)-butyrate (16).** A solution of 25 g (0.12 mol) of ethyl 2-(3'-methyl-4'-pyridyl)-butyrate (15) in 25 ml of dry THF was added dropwise to a solution of 20.2 g (0.18 mol) of potassium t-butoxide in 100 ml of THF at -40° (acetonitrile-Dry Ice) under a nitrogen atmosphere. Stirring was continued for 15 min, and then dry oxygen was passed through the solution for 2 hr. The reaction mixture was poured into 100 ml of 20% NH$_4$Cl solution, and the aqueous layer was extracted with two 50 ml portions of ether. The organic layer and ether extracts were combined, washed with brine, and dried ($MgSO_4$). The solution was concentrated under reduced pressure to give an oil which solidified with scratching under pentane. The white solid was collected and dried to give 23.9 g (83%) of 16, mp 90-93°. An analytical sample, mp 96-97°, was prepared by two recrystallizations from CCl$_4$-hexane: ir (Appendix A, Figure 1); nmr (Appendix B, Figure 1).

**Anal. Calcd for $C_{12}H_{17}NO_4$:** C, 60.24; H, 7.17; N, 5.85. Found: C, 60.37; H, 7.16; N, 5.87.
Preparation of Ethyl 2-Hydroxy-2-(3'-methyl-4'-pyridyl)-butyrate (17) from Ethyl-2-hydroperoxy-2-(3'-methyl-4'-pyridyl)-butyrate (16). A solution of 20.0 g (83.6 mmol) of 17 in 50 ml of methanol was added to a solution of 58.1 g (0.35 mol) of KI in 200 ml of methanol and 50 ml of acetic acid. The mixture was stirred at room temperature for 5 hr and then concentrated under reduced pressure. The residual liquid was poured into 100 ml of ice water and treated with 100 ml of saturated Na₂S₂O₃ solution. The resulting solution was made basic with 10% NaOH and extracted with five 50 ml portions of CHCl₃. The extracts were washed with brine, dried (K₂CO₃), and concentrated to give a yellow oil. The crude product solidified with scratching under pentane to give 17.26 g (92%) of 17 as a light tan solid. Recrystallization from cyclohexane gave 15.66 g (84%) of 17 as white crystals, mp 110-111° (lit. 109-111°); ir and nmr (identical to that of an authentic sample).

Preparation of Ethyl 2-(2'-o-Tolyl-5'-methyl-4'-pyridyl)-butyrate (40). A solution of 20.74 g (0.10 mol of ethyl 2-(3'-methyl-4'-pyridyl)-butyrate (15) in 200 ml of dry THF was cooled in a carbon tetrachloride-Dry Ice bath. Ethyl chloroformate (11.18 g, 0.1 mmol) was added dropwise over 5 min to the stirred solution. A solution of o-tolyl-magnesium bromide (0.11 m) in 100 ml of THF was added dropwise at a rate to keep the internal temperature below 0°C. After the addition was complete, the mixture was stirred at
0-5°C (Ice Bath) for 1 hr and then was hydrolyzed with 100 ml of 20% NH₄Cl solution. The aqueous layer was extracted with 50 ml of ether, and the extract was added to the organic layer. The organic layer was washed with two 50-ml portions of 10% HCl, 50 ml of water, and 75 ml of brine, and then was dried (K₂CO₃). Concentration of the solution under reduced pressure gave 29.16 g of a yellow oil. The crude oil was treated with 2.52 g (78.6 mmol) of sublimed sulfur at 200° for 40 min. The reaction mixture was cooled, dissolved in 200 ml of ether, and filtered through a Florosil pad. The filtrate was extracted with four 50 ml portions of 10% HCl. The acid extracts were washed with 50 ml of ether, cooled and made basic with 20% NaOH, and extracted with four 50 ml portions of ether. The extracts were washed with brine, dried (K₂CO₃), and evaporated to give a brown oil. The crude product was treated with hot CHCl₃-Norite, filtered, concentrated, and distilled to give 17.8 g (60%) of 40 as a yellow oil, bp 143-152°/0.3 mm; ir (Appendix A, Figure 13); nmr (Appendix B, Figure 13). The acid extracts were made basic with 20% NaOH and extracted with two 50 ml portions of ether. The ether extracts were washed with brine, dried (K₂CO₃), and concentrated to give 6.02 g (29%) of 15 as a yellow oil. The yield of 40 based on the recovered starting material 15 was 84%.

Anal. Calcd for C₁₉H₂₃N₁O₂:  C, 76.73; H, 7.80; N, 4.71. Found:  C, 76.47; H, 7.66; N, 4.94.
Preparation of Ethyl 2-Hydroxy-2-(2'-o-tolyl-5'-methyl-4'-pyridyl)-butyrate (41). A solution of 17.37 g (58.4 mmol) of 40 in 60 ml of THF was added dropwise to a solution of 9.83 g (87.6 mmol) of potassium t-butoxide in 100 ml of THF at -40° (acetonitrile-Dry Ice bath) under a nitrogen atmosphere. Stirring was continued for 15 min, and then dry oxygen was passed through the solution for 1.5 hr. The reaction mixture was poured into 100 ml of 20% NH₄Cl solution, and the aqueous layer was extracted with three 50-ml portions of ether. The organic layer and ether extracts were combined, washed with brine, and concentrated. The residue was dissolved in 250 ml of methanol and treated with 38.8 g (0.23 mol) of KI and 50 ml of acetic acid. The mixture was stirred at room temperature for 18 hr and then concentrated under reduced pressure. To the residue was added 100 ml portions of water, CHCl₃, and saturated Na₂S₂O₃ solution. The mixture was made basic with 10% NaOH solution with cooling, and then the aqueous layer was extracted with three 75 ml portions of CHCl₃. The organic layer and CHCl₃ extracts were combined, washed with water and brine, and dried (K₂CO₃). Concentration under reduced pressure gave a yellow oil which solidified with scratching under pentane to give 17.03 g (93%) of 41 as a white solid. Recrystallization from 2-propanol gave a white solid, mp 121-123.5°; ir (Appendix A, Figure 14); nmr (Appendix B, Figure 14). This material was contaminated with a small amount of the
methyl ester, which was formed via transesterification during the reaction. This can be avoided by the use of acetic acid as the solvent as in the preparation of 56. An analytical sample, mp 124-125°, was prepared by further recrystallizations from 2-propanol.

Anal. Calcd for C_{19}H_{23}NO_{3}: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.61; H, 7.42; N, 4.58.

Preparation of Ethyl 2-Hydroxy-2-(2'-o-tolyl-5'-methyl-4'-pyridyl)-butyrate N-oxide (42). A solution of 9.32 g (29.74 mmol) of 41 and 10.26 g (59.48 mmol) of 85% m-chloroperbenzoic acid in 150 ml of CHCl₃ was allowed to stand in the dark at room temperature for 5 days. The reaction mixture was diluted with 100 ml of CHCl₃, was washed with four 75-ml portions of 5% NaOH, 75 ml of water, and 75 ml of brine, and was dried (K₂CO₃). Concentration under reduced pressure gave a solid residue which was washed with two 50 ml portions of ether to give 8.75 g (89%) of 42 as a white solid, mp 139-144°; ir (Appendix A, Figure 15); nmr (Appendix B, Figure 15). An analytical sample, mp 147-147.5°, was prepared by two recrystallizations from cold anhydrous ether.

Anal. Calcd for C_{19}H_{23}NO₄: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.48; H, 7.00; N, 4.28.

Preparation of Ethyl 2-Hydroxy-2-(2'-o-tolyl-5'-methyl-6'-chloro-4'-pyridyl)-butyrate (43). To 7.0 g (21.25 mmol) of 42 was added 75 ml of POCl₃. The mixture
was heated at gentle reflux for 45 min and then concentrated under reduced pressure. To the residual liquid was added 100 ml of ice water and 75 ml of CHCl₃. The mixture was made basic with 5% NaOH solution and the aqueous layer was extracted with three 50-ml portions of CHCl₃. The extracts were washed with 50 ml of water, two 25-ml portions of 5% HCl, 50 ml of water, and 50 ml of brine and was dried (K₂CO₃). The solution was concentrated under reduced pressure to give 5.09 g (69%) of 43 as a yellow oil. The oil was extracted with hot hexane, and the extracts were cooled (0°). Filtration and concentration of the filtrate gave 43 as an analytically pure clear oil: ir (Appendix A, Figure 16); nmr (Appendix B, Figure 16).

**Anal.** Calcd for C₁₉H₂₂ClNO₃: C, 65.61; H, 6.38; N, 4.03. Found: C, 65.45; H, 6.14; N, 4.12.

**Attempted Bromination of 43 with NBS.** A mixture of 0.5 g (1.44 mmol) of 43, 0.54 g (3.02 mmol) of recrystallized NBS, 50 mg of dibenzoyl peroxide, and 50 ml of CCl₄ was heated under reflux for 1 hr by means of a 100-watt bulb. The mixture was cooled in an ice bath and filtered. The filter cake was washed with CCl₄, and the filtrate was concentrated under reduced pressure to give 0.4 g of a yellow oil. This oil was shown by nmr to be mainly starting material 43 with the absence of any methyl-brominated products.
Preparation of Ethyl 2-(2'-o-Methoxymethylphenyl-5'-methyl)-4'-pyridyl-butyrate (45). Using the procedure for the preparation of 40, 20.73 g (0.1 mol) of ethyl 2-(3'-methyl-4'-pyridyl)-butyrate (15), 15.66 g (0.1 mol) of phenyl chloroformate, and 0.11 mol of o-methoxymethylphenylmagnesium bromide in 100 ml of THF gave 36.3 g of a yellow oil. The oil was treated with 2.57 g (0.08 mol) of sublimed sulfur at 200-210° for 45 min, cooled, dissolved in 150 ml of ether, and placed over K₂CO₃ overnight. The dark mixture was filtered through a Florisil pad and the filtrate was extracted with five 50-ml portions of 10% HCl. The acid extracts were washed with ether, cooled, made basic with 10% NaOH, and extracted with ether. The extracts were washed with water and brine and dried (K₂CO₃). The solution was concentrated to give a brown oil which was treated with CHCl₃-Norite and filtered. The filtrate was concentrated, and the residual oil distilled to give 12.9 g of a dark oil, bp 150-167°/0.05 mm. The oil was separated into two major components by HPLC (Silica Gel; CHCl₃/EtOAc (10/1)). The first major fraction gave 7.96 g (24%) of 45 as an analytically pure clear oil; ir (Appendix A, Figure 17); nmr (Appendix B, Figure 17).

Anal. Calcd for C₂₀H₂₅N₁O₃:  C, 73.37; H, 7.70; N, 4.28. Found:  C, 73.47; H, 7.90; N, 4.36.

The second major fraction gave 3.9 g (12%) of 46 as an analytically pure clear oil; ir (Appendix A, Figure
Preparation of Ethyl 2-Hydroxy-2-(2'-o-methoxymethylphenyl-5'-methyl-4'-pyridyl)-butyrate \( (\mathbf{47}) \). Using the procedure for the preparation of \( \mathbf{41} \), 7.68 g (22.36 mmol) of \( \mathbf{45} \), 3.76 g (33.54 mmol) of potassium t-butoxide, oxygen (1.5 hr), and 13.41 g (89.4 mmol) of NaI in 200 ml of acetic acid gave crude \( \mathbf{47} \) as a dark yellow oil. The crude product was purified by HPLC (Silica gel; CHCl\(_3\)/EtOAc (10/1)) to give 5.57 g (73%) of \( \mathbf{47} \) as an analytically pure viscous yellow oil; ir (Appendix A, Figure 19); nmr (Appendix B, Figure 19).

Preparation of Ethyl 2-Hydroxy-2-(2'-o-methoxymethylphenyl-5'-methyl-4'-pyridyl)-butyrate N-Oxide \( (\mathbf{48}) \). A solution of 5.5 g (16.0 mmol) of \( \mathbf{47} \) and 4.15 g (24.0 mmol) of 85% m-chloroperbenzoic acid in 100 ml of CHCl\(_3\) was allowed to stand in the dark at room temperature for 5.5 days. The reaction mixture was diluted with 75 ml of CHCl\(_3\), was washed with three 50-ml portions of 5% NaOH, 50 ml of water and 50 ml of brine, and was dried (K\(_2\)CO\(_3\)). Concentration under reduced pressure gave a viscous oil as residue which was purified by HPLC (Silica gel; CH\(_2\)Cl\(_2\)/EtOH (9/1)) to give 5.14 g (89%) of \( \mathbf{48} \) as a viscous tan oil; ir (Appendix A, Figure 20); nmr (Appendix B, Figure 20).
Anal. Calcd for C_{20}H_{25}NO_{5}: C, 66.84; H, 7.01; N, 3.90.  Found: C, 67.10; H, 7.10; N, 3.90.

Preparation of 2-(p-Chlorophenyl)-4,5-dimethylpyridine-N-oxide (32). To 14.0 g (64.31 mmol) of 2-(p-chlorophenyl)-4,5-dimethylpyridine (31) was added 100 ml of 40% peroxymetric acid. The mixture was heated in an oil bath at 70-80° for 8 hr, 25 ml of 30% hydrogen peroxide solution was added, and heating (70-80°) was continued for 9 hr. The reaction mixture was concentrated under reduced pressure, and 75 ml portions of 5% NaOH and CHCl_{3} were added to the residual liquid. The stirred mixture was made basic by the addition of 10% NaOH. The CHCl_{3} layer was collected, and the aqueous layer was extracted with three 50 ml portions of CHCl_{3}. The combined CHCl_{3} extracts were washed with brine, dried (K_{2}CO_{3}), and concentrated to give a yellow oil which solidified with scratching under pentane. The solid was suspended in 50 ml of boiling pentane and filtered hot to give 10.73 g (71%) of 2-(p-chlorophenyl)-4,5-dimethylpyridine-N-oxide (32) as a white solid, mp 121-124°. The pentane washings were cooled and 2.70 g (19%) of 2-(p-chlorophenyl)-4,5-dimethylpyridine (31) precipitated as white crystals, mp 57-59°.

An analytical sample of 32 was prepared by recrystallization from cyclohexane to give a white solid, mp 131.5-132.5°; ir (Appendix A, Figure 7); nmr (Appendix B, Figure 7).

Anal. Calcd for C_{13}H_{12}NOCl: C, 66.81; H, 5.18; N, 5.99.  Found: C, 66.80; H, 5.15; N, 6.01.
Preparation of 2-(p-Chlorophenyl)-4,5-dimethyl-6-chloropyridine (33). To 12.06 g (51.6 mmol) of 2-(p-chlorophenyl)-4,5-dimethylpyridine-N-oxide (32) was added 140 ml of POC\(_3\). The mixture was heated at 110-115° for 1.5 hr and then concentrated under reduced pressure. The residual liquid was rinsed onto crushed ice with CHCl\(_3\), and the aqueous layer was extracted with three 75 ml portions of CHCl\(_3\). The combined extracts were washed with 50 ml portions of 5% NaOH solution, water, and brine and was dried (K\(_2\)CO\(_3\)). Concentration under reduced pressure gave a solid residue which recrystallized from 95% ethanol to give 8.24 g (63%) of 33 as white crystals, mp 96-98°. An analytical sample, mp 99.5-100.5°, was prepared by two recrystallizations from 95% ethanol; ir (Appendix A, Figure 8); nmr (Appendix B, Figure 8).


Preparation of 2-(p-Chlorophenyl)-4,5-dimethyl-6-methoxypyridine (34). A mixture of 8.24 g (32.7 mmol) of 2-(p-chlorophenyl)-4,5-dimethyl-6-chloropyridine (33) and 4.18 g (77.4 mmol) of sodium methoxide in 60 ml of dry DMSO was heated with stirring at 80° in an oil bath for 17 hr under a nitrogen atmosphere. The solution was cooled, poured into 150 ml of water, and extracted with five 50-ml portions of ether. The ether extracts were washed with water and brine, were dried (K\(_2\)CO\(_3\)) and were concentrated
to give a quantitative yield of crude 34 as a tan solid, mp 71-74°. Recrystallization from 95% ethanol gave 6.34 g (78%) of 34 as white crystals, mp 77-78°. An analytical sample, mp 79-79.5°, was prepared by two additional recrystallizations from 95% ethanol; ir (Appendix A, Figure 9); nmr (Appendix B, Figure 9).

**Anal.** Calcd for C_{14}H_{14}ClNO: C, 67.88; H, 5.70; N, 5.65. Found: C, 67.98; H, 5.81; N, 5.59.

**Preparation of Ethyl 2-(2'-p-Chlorophenyl-5'-methyl-6'-methoxy-4'-pyridyl)-butyrate (35).** Under a positive pressure of N₂, a solution of 4.96 g (48.99 mmol) of diisopropylamine in 50 ml of anhydrous THF was stirred at -70° (isopropanol-Dry Ice) while 21.4 ml (48.99 mmol) of 2.29 M n-BuLi in hexane was added during 10 min. The mixture was stirred for 15 min. A solution of 5.78 g (23.33 mmol) of 2-(p-chlorophenyl)-4,5-dimethyl-6-methoxypyridine (34) in 30 ml of THF was added dropwise over a period of 5 min, and stirring was continued for 10 min. Then 4.13 g (35.0 mmol) of diethyl carbonate in 10 ml of THF was added dropwise. The cooling bath was removed and stirring was continued for 30 min. Ethyl iodide (4.73 g, 30.33 mmol) was added, and stirring was continued at room temperature for 2 hr. The reaction mixture was hydrolyzed with 50 ml of water, and 100 ml of ether was added. The organic layer was washed with two 50-ml portions of water and 50 ml of brine, and after drying (K₂CO₃), the layer was concentrated under reduced
pressure. The residual liquid was purified by HPLC (Silica gel; HEX/CHCl₃ (10/1)) to give 6.12 g (75%) of 35 as a clear oil; ir (Appendix A, Figure 10); nmr (Appendix B, Figure 10).

Anal. Calcd for C₁₉H₂₂ClNO₃: C, 65.61; H, 6.38; N, 4.03. Found: C, 65.90; H, 6.61; N, 4.10.

Preparation of Ethyl 2-(2'-p-Chlorophenyl-5'-bromo-methyl-6'-methoxy-4'-pyridyl)-butyrate (36). A mixture of 6.0 g (17.25 mmol) of 35, 3.38 g (18.98 mmol) of recrystallized NBS, 0.3 g of dibenzoyl peroxide, and 150 ml of CCl₄ was heated under reflux for 4 hr by means of a 100-watt bulb. The mixture was cooled in an Ice Bath and filtered. The filter cake was washed with 50 ml of CCl₄, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 50 ml of Hexane and placed in a freezer (0°) overnight. A small amount of solid was removed by filtration, and the filtrate was concentrated to give 7.29 g (99%) of 36 as a viscous yellow oil; ir (Appendix A, Figure 11); nmr (Appendix B, Figure 11). Due to the reactive nature of the compound, elemental analyses were determined without further purification.


Preparation of 6-p-Chlorophenyl-4-ethyl-8-methoxy-3-oxo-1H-pyrano-[3,4-c]pyridine (37). To a solution of 6.72 g (15.75 mmol) of 36 in 100 ml of MEK under a N₂ atmosphere was added 4.91 g (50 mmol) of potassium acetate. The mixture
was heated under reflux for 3 hr and cooled. Ether (100 ml) was added, and the resulting mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was dissolved in 100 ml of DME. To this solution was added 75 ml of 2N H₂SO₄, and the mixture was heated under reflux for 16 hr under a N₂ atmosphere. The reaction mixture was cooled, poured into 200 ml of ice water, neutralized with 10% NaHCO₃, and extracted with four 75 ml portions of CH₂Cl₂. The extracts were washed with water and brine and were dried (MgSO₄). Concentration of the extracts under reduced pressure gave 4.65 g (93%) of 37 as a tan oil. The oil was dissolved in 40 ml of hot 95% ethanol, filtered, and cooled in a freezer (0°) to give 3.5 g (70%) of 37 as a tan solid, mp 119-122°; ir (Appendix A, Figure 12); nmr (Appendix B, Figure 12). An analytical sample, mp 127.5-128°, was prepared by three additional recrystallizations from 95% ethanol.

Anal. Calcd for C₁₇H₁₆ClNO₃:  C, 64.26; H, 5.08; N, 4.41. Found:  C, 64.42; H, 5.23; N, 4.72.

Preparation of 2-Amino-3,4-(4,5)-dimethylpyridine (52). A mixture of 107.16 g (1.0 mol) of 3,4-lutidine and 46.81 g (1.2 mol) of NaN₃ in 260 g of dimethylaniline was heated at 160° in an oil bath for 8 hr under a nitrogen atmosphere. The reaction mixture was cooled and slowly hydrolyzed by the dropwise addition of 200 ml of water. The aqueous layer was extracted with two 100 ml portions of ether. The ether extracts were washed with brine and con-
centrated under reduced pressure. The residue was added to the original organic layer, and the combined mixture was dried (K₂CO₃). Most of the dimethylaniline and unreacted 3,4-lutidine were removed by distillation under reduced pressure (bp 90-119°/14 mm). The residual liquid was transferred to a smaller apparatus and the distillation was continued, bp 124-130°/14 mm (lit. bp 124°/10 mm) to give 48.6 g (40%) of (52) as a white solid. It was determined from the nmr spectrum of the product that the ratio of (52a)/(52b) was 4/1.

Preparation of 2-Bromo-3,4-dimethylpyridine (53). A solution of 33.7 g (0.28 mol) of 52 in 150 ml of 48% HBr was cooled in a CCl₄-Dry Ice bath while 40 ml of bromine was added. The mixture was stirred while a solution of 45 g of NaNO₂ in 75 ml of water was added dropwise such that the internal temperature did not rise above 5°. The cooling bath was removed and stirring was continued for 30 min. A solution of 100 g of NaOH in 250 ml of water was added dropwise with external cooling. The mixture was extracted with ether, and the ether extracts were washed with brine, dried over K₂CO₃, and concentrated to give a red oil. The crude oil was dissolved in 25 ml of hexane and cooled (-24°). The tan crystals which formed were collected by filtration. The filtrate was concentrated and the process repeated to give 20.87 g (40%) of 2-bromo-3,4-dimethylpyridine (53): mp 41-43° (lit. mp 49-50°).
Preparation of 2-Methoxy-3,4-dimethylpyridine (54a).

To a solution of 20.0 g (0.11 mol) of 2-bromo-3,4-dimethylpyridine (53) in 100 ml of dry DMSO was added 11.88 g (0.22 mol) of sodium methoxide. The mixture was heated with stirring at 75° in an oil bath for 5 hr under a nitrogen atmosphere. The solution was cooled, poured into 200 ml water, and extracted with five 50-ml portions of ether. The ether extracts were washed with brine, dried (K₂CO₃) and concentrated and the residual liquid was distilled to give 13.05 g (87%) of 54a as a clear oil; bp 70-77°/15 mm; ir (Appendix A, Figure 21a); nmr (Appendix B, Figure 21a).

A small sample of 54a was treated with refluxing HBr/acetic acid to give 3,4-dimethyl-2-pyridone (54b) as a white solid. Recrystallization of the solid from benzene gave 54b as white crystals, mp 182.5-183°; ir (Appendix A, Figure 21b); nmr (Appendix B, Figure 21b).


Preparation of Ethyl 2-(2'-Methoxy-3'-methyl-4'-pyridyl)-butyrate (55). Under a positive pressure of N₂, a solution of 20.24 g (0.20 mol) of diisopropylamine in 100 ml of anhydrous THF was stirred at -70° (isopropanol-Dry Ice) while 87.4 ml (0.20 mol) of 2.29 M n-BuLi in hexane was added over 10 min and allowed to stand for 15 min. A solution of 13.0 g (94.77 mmol) of 2-methoxy-3,4-dimethylpyridine (54a)
in 50 ml of THF was added dropwise over a period of 5 min and stirring was continued for 15 min. Then 16.54 g (0.14 mol) of diethyl carbonate in 20 ml of THF was added dropwise. The cooling bath was removed and stirring was continued for 30 min. Ethyl iodide (18.72 g, 0.12 mol) was added and stirring was continued at room temperature for 1.5 hr. The reaction mixture was hydrolyzed with 75 ml of water, and the aqueous layer was extracted with 75 ml of ether. The organic layers were combined, washed with water and brine, dried (K₂CO₃), and concentrated under reduced pressure. The residual liquid was distilled to give 15.96 g (71%) of 55 as a clear oil, bp 85-95°/0.1 mm; ir (Appendix A, Figure 22); nmr (Appendix B, Figure 22).


Preparation of Ethyl 2-Hydroxy-2-(2'-methoxy-3'-methyl-4'-pyridyl)-butyrate (56). A solution of 15.0 g (63.21 mmol) of ethyl 2-(2'-methoxy-3'-methyl-4'-pyridyl)-butyrate (55) in 25 ml of THF was added dropwise to a solution of 10.64 g (94.82 mmol) of potassium t-butoxide in 100 ml of THF at -40° (acetonitrile-Dry Ice) under a nitrogen atmosphere. Stirring was continued for 15 min, and then dry oxygen was passed through the solution for 1.5 hr. The reaction mixture was poured into 100 ml of 20% NH₄Cl solution, and the aqueous layer was extracted with three 50-ml portions of ether. The organic layer and ether extracts were com-
bined, washed with brine, and concentrated under reduced pressure. The residue was dissolved in 300 ml acetic acid and treated with 37.47 g (0.25 mol) of sodium iodide. The mixture was stirred at room temperature for 6 hr and concentrated under reduced pressure. To the residue was added 100 ml portions of water, CHCl₃, and saturated Na₂S₂O₃ solution. The mixture was made slightly basic with 10% NaOH solution, and the aqueous layer was extracted with three 75 ml portions of CHCl₃. The organic layer and CHCl₃ extracts were combined, washed with brine, dried (K₂CO₃), and concentrated under reduced pressure. The residual liquid was dissolved in 100 ml hexane, the solution cooled (0°) and filtered, and the filtrate concentrated to give 14.42 g (90%) of 56 as an analytically pure clear oil. ir (Appendix A, Figure 23); nmr (Appendix B, Figure 23).

Anal. Calcd for C₁₃H₁₉NO₄: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.79; H, 7.79; N, 5.65.

Preparation of Ethyl 2-Hydroxy-2-(2'-methoxy-3'-bromomethyl-4'-pyridyl)-butyrate (57). A mixture of 13.0 g (51.32 mmol) of ethyl 2-hydroxy-2-(2'-methoxy-3'-methyl-4'-pyridyl)-butyrate (56), 10.05 g (56.45 mmol) of recrystallized NBS, 0.5 g of dibenzoyl peroxide, and 250 ml of CCl₄ was heated under reflux for 4 hr by means of a 100-watt bulb. The mixture was cooled in an ice bath and filtered. The filter cake was washed with two 50 ml portions of CCl₄, and the filtrate was concentrated under reduced pressure. The
residue was extracted with 300 ml of boiling petroleum ether (bp 30-60°). The extracts were filtered and the filtrate was concentrated to give 17.0 g (99.7%) of 57 as a yellow oil, ir (Appendix A, Figure 24); nmr (Appendix B, Figure 24). Due to the reactive nature of the compound, an analytical sample was submitted without further purification.

Anal. Calcd for C_{13}H_{18}NO_{4}Br: C, 47.00; H, 5.46; N, 4.22. Found: C, 47.48; H, 5.62; N, 4.40.

Preparation of Ethyl 2-Hydroxy-2-(2'-methoxy-3'-acetoxyethyl-4'-pyridyl)-butyrate (58). To a solution of 1.1 g (3.31 mmol) of 57 in 25 ml of methylethyl ketone under a N₂ atmosphere was added 0.97 g (9.93 mmol) of potassium acetate. The mixture was heated under reflux for 1 hr and concentrated under reduced pressure. Water (50 ml) was added to the residue, and the resulting mixture was extracted with CHCl₃. The CHCl₃ extracts were washed with brine, dried (K₂CO₃), treated with Norit, and filtered through a Florisil pad. The filtrate was concentrated to give 0.91 g (88%) of 58 as a yellow oil which solidified with scratching under hexane. Recrystallization of the solid from cyclohexane gave 58 as white crystals, mp 75.5-76°C. ir (Appendix A, Figure 25); nmr (Appendix B, Figure 25).

Anal. Calcd for C_{15}H_{21}NO_{6}: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.87; H, 6.67; N, 4.56.
Preparation of 7-Methoxypyrido(5,4-c)2-oxo-3-ethyl-3-hydroxy-3,6-dihydropyran (50). To a solution of 17.0 g (51.17 mmol) of 57 in 350 ml methylethyl ketone (MEK) under a N₂ atmosphere was added 14.72 g (0.15 mol) of potassium acetate. The mixture was heated under reflux for 2 hr and cooled, 100 ml of ether was added, and the resulting mixture was filtered. The filtrate was concentrated under reduced pressure to give a tan oil which was taken up in 200 ml of DME. To the solution was added 200 ml of 2.5 N H₂SO₄, and the mixture was heated under reflux for 19 hr. The reaction mixture was cooled, poured into 100 ml of ice water, neutralized with 10% NaHCO₃ solution, and extracted with five 75 ml portions of CHCl₃. The extracts were washed with water and brine and dried (MgSO₄). The dark solution was treated with Norit, filtered through a Florisil pad, and the filtrate was concentrated under reduced pressure to give 6.87 g (60%) of 50 as a dark yellow oil. The oil solidified under hot hexane and was recrystallized from cyclohexane to give 4.74 g (41%) of 50 as a tan solid, mp 100.5-102°. ir (Appendix A, Figure 26); nmr (Appendix B, Figure 26).
Preparation of 7-Methoxypyrido(5,4-c)2-oxo-3-ethyl-3-hydroxy-3,6-dihydropyran (50) from 2-Chloro D and E Ring Analog 10. A mixture of 1.18 g (5.18 mmol) of 10 and 1.4 g (25.9 mmol) of sodium methoxide in 40 ml of DMSO was heated at 90° for 18 hr under nitrogen. The mixture was cooled, poured into 100 ml of water, acidified with 10% HCl, and stirred at room temperature for 4 hr. The solution was neutralized with solid NaHCO₃ and extracted with four 50 ml portions of ether. The ether extracts were washed with 50 ml of water and 50 ml of brine and were dried (MgSO₄). Concentration of the solution under reduced pressure gave 0.8 g (69%) of 50 as a yellow oil which solidified under pentane to give white crystals, mp 98-103°. An analytical sample was prepared by two recrystallizations from hexane to give 50 as white needles, mp 107-108°; ir (Appendix A, Figure 26); nmr (Appendix B, Figure 26).


Preparation of Ethyl 2-(2'-Methoxy-3'-bromomethyl-4'-pyridyl)-butyrate (59). Using the procedure for the preparation of 57, 17.5 g (73.75 mmol) of ethyl 2-(2'-methoxy-3'-methyl-4'-pyridyl)-butyrate (55), 14.44 g (81.13 mmol) of NBS, 1.0 g of dibenzoyl peroxide and 300 ml of CCl₄ gave 23.2 g (99.5%) of 59 as a viscous yellow oil, ir (Appendix A, Figure 27); nmr (Appendix B, Figure 27). Due
to the reactive nature of the compound, analyses were determined without further purification.

**Anal.** Calcd for C_{13}H_{18}BrNO_{3}: C, 49.38; H, 5.74; N, 4.43. Found: C, 49.30; H, 5.58; N, 5.07.

**Preparation of 7-Oxopyrido(5,4-c)2-oxo-3-ethyl-3,6-dihydropyran (60).** A solution of 5.0 g (15.8 mmol) of 59 in 30 ml of 48% HBr was heated at reflux for 2 hr and concentrated under reduced pressure. Water (20 ml) and CHCl_{3} (50 ml) were added to the cooled residue. Saturated sodium bicarbonate solution (10%) was added dropwise until the aqueous layer was slightly basic and the layers were separated. The aqueous layer was extracted with CHCl_{3} and the combined CHCl_{3} extracts were washed with brine and dried (MgSO_{4}). The solution was concentrated under reduced pressure to give, after drying, 1.85 g (61%) of 60 as a white solid, mp 202-204°d; ir (Appendix A, Figure 28); nmr (Appendix B, Figure 28). An analytical sample was obtained by one recrystallization of the solid from CHCl_{3}-hexane to give 60 as white crystals: mp 207-208°d.

**Anal.** Calcd for C_{10}H_{11}NO_{3}: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.91; H, 5.99; N, 7.14.

**Preparation of Diethyl 1-Cyanoethanephosphonate (67).** A solution of 2.75 g (0.05 mmol) of propionitrile in 25 ml of THF was added dropwise over 5 min to a cooled (-70°) solution of LDA in 100 ml of THF-HEXANE. The mixture was stirred for 30 min; then 8.63 g (0.05 mmol) of diethylchloro-
phosphate was added dropwise such that the internal temperature did not rise above -60°. The solution was stirred 30 min after the addition. The cooling bath was removed and stirring was continued for an additional 30 min. The reaction mixture was hydrolyzed with 50 ml of 20% NH₄Cl solution and the layers were separated. The organic layer was washed with water and brine and was dried (MgSO₄). Concentration of the solution under reduced pressure gave an oil which was distilled to give 6.0 g (63%) of 67 as a cloudy oil, bp 85-89°/0.3 mm (lit. 87-89°/0.3 mm). The cloudiness was caused by a small amount of an impurity which codistilled with the product. The impurity did not interfere with the subsequent reaction.

Preparation of 2-o-Nitrobenzylidene)propionitrile

(68). A solution of 5.0 g (26.15 mmol) of diethyl 1-cyanoethanephosphonate (67) in 25 ml of THF was added dropwise to a solution of 3.23 g (28.77 mmol) of potassium t-butoxide in 75 ml of THF at room temperature and stirred for 30 min. o-Nitrobenzaldehyde (3.95 g, 26.15 mmol) in 25 ml of THF was added dropwise and the resulting mixture was allowed to stand at room temperature for 4 hr. Water (300 ml) and 100 ml of ether were added and the aqueous layer was extracted with three 75-ml portions of ether. The combined extracts were washed with water and brine and were dried (MgSO₄). The solution was treated with Norite at room temperature and filtered through a Florcil pad to give a yellow filtrate. Concentration under
reduced pressure gave a yellow oil which solidified on standing to give 4.2 g (85%) of 68 as a tan solid. A small sample was recrystallized from methanol to give 68 as light yellow crystals, mp 112-113° (lit. mp 115°).

Preparation of 2-Amino-3-methylquinoline (69). To 10.25 g (54.5 mmol) of crude 68 in 150 ml of methanol was added 38.3 g (0.22 mol) of sodium dithionite (Na2S2O4) and 150 ml of water. The mixture was heated under reflux for 3 hr, then most of the methanol was removed under reduced pressure. Saturated K2CO3 (100 ml) was added to the concentrate and the solution was extracted with six 75-ml portions of CHCl3. The extracts were washed with brine, dried (K2CO3), and concentrated to give 3.7 g (43%) of 69 as a yellow solid. An analytical sample, mp 164-165°, was prepared by two recrystallizations from carbon tetrachloride; ir (Appendix A, Figure 29); nmr (Appendix B, Figure 29).


Preparation of 1-(3'-Methyl-2'-quinolyl)-succinimide (70). A mixture of 3.7 g (23.4 mmol) of crude 2-amino-3-methylquinoline (69) and 2.81 g (28.1 mmol) of succinic anhydride was heated slowly to 170° and maintained at that temperature for 2 hr under a stream of nitrogen. The mixture was cooled, dissolved in 100 ml of CHCl3, treated with Norite, and filtered through a Florisil pad. After two additional treatments with Norite, the filtrate was concentrated under reduced pressure to give 3.16 g (56%) of 70 as a tan solid,
mp 173-174°; ir (Appendix A, Figure 30); nmr (Appendix B, Figure 30). An analytical sample of 70, mp 173-174°, was prepared by one recrystallization from CHCl₃-HEXANE.

**Anal. Calcd for C₁₄H₁₂N₂O₂:** C, 69.99; H, 5.03; N, 11.66. **Found:** C, 69.86; H, 5.21; N, 11.46.

**Preparation of 1-(3'-Bromomethyl-2'-quinolyl)-succinimide (71).** A mixture of 1.0 g (41.6 mmol) of 70, 0.82 g (4.6 mmol) of NBS, and 50 mg of dibenzoyl peroxide in 50 ml of dry ethylene chloride was heated under reflux by means of a 100 watt lamp for 17 hr. The solution was concentrated under reduced pressure to give a oily residue. The residue was shown by nmr to contain succinimide, 71, and starting material (70) with a product/starting material ratio of about 75/25. Purification by HPLC (silica gel; isopropanol/CHCl₃(10/1)) gave 0.7 g (53%) of 71 as a low melting tan solid; ir (Appendix A, Figure 31); nmr (Appendix B, Figure 31). An analytical sample was prepared by one recrystallization from ether to give 71 as white crystals, mp (softens 120°, mp 141.5-142.5°).

**Anal. Calcd for C₁₄H₁₁BrN₂O₂:** C, 52.69; H, 3.47; N, 8.78. **Found:** C, 52.95; H, 3.56; N, 8.73.
REFERENCES


27. Reference 22, p 111.


37. Reference 22, p 59.

38. Reference 5, Appendix A, Figure 2.

39. Reference 5, Appendix B, Figure 2.

40. Reference 11, p 51.

41. This reaction was done by D. P. Kelley of the Chemistry Department, University of New Hampshire.


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Figure 2 (neat). Compound (24).
Figure 3 (neat). Compound (25).
A-Figure 4 (neat). Compound (26).
A-Figure 5 (KBr). Compound (27).
A-Figure 6 (KBr). Compound (28).
A—Figure 7 (KBr). Compound (32).
Figure 8 (KBr). Compound (33).
A-Figure 9 (KBr). Compound (34).
A-Figure 10 (neat). Compound (35).
A-Figure 11 (neat). Compound (36).
A-Figure 12 (KBr). Compound (37).
Figure 13 (neat). Compound (40).
A-Figure 14 (KBr). Compound (41).
A-Figure 15 (KBr). Compound (42).
Figure 16 (neat). Compound (43).
A-Figure 17 (neat). Compound (45).
A-Figure 18 (neat). Compound (46).
A-Figure 19 (neat). Compound (47).
A-Figure 20 (neat). Compound (48).
A-Figure 21a (neat). Compound (54a).
A-Figure 21b (KBr). Compound (54b).
Figure 22 (neat). Compound (55).
A-Figure 23 (neat). Compound (56).
A-Figure 24 (neat). Compound (57).
A-Figure 25 (KBr). Compound (58).
A-Figure 26 (KBr). Compound (50).
A-Figure 28 (KBr). Compound (60).
A-Figure 29 (KBr). Compound (69).
A-Figure 30 (KBr). Compound (70).
A-Figure 31 (KBr). Compound (71).
APPENDIX B

NUCLEAR MAGNETIC RESONANCE SPECTRA
Figure 1 (CDCl₃). Compound (16).
Figure 2 (CDCl₃). Compound (24).
B-Figure 3 (CDCl₃). Compound (25)
B-Figure 4: (CDCl₃). Compound (26).
B-Figure 5 (CF$_3$COOH). Compound (27).
B-Figure 6 (CDCl$_3$). Compound (28).
B-Figure 7 (CDCl₃). Compound (32).
B-Figure 8 (CDCl₃). Compound (33).
B-Figure 9 (CDCl$_3$). Compound (34).
B-Figure 10 (CDCl₃). Compound (35).
Figure 11 (CDCl3): Compound (36)
B-Figure 12 (CDCl₃): Compound (37).
B—Figure 13 (CDCl₃). Compound (40).
B-Figure 14 (CDCl₃). Compound (41).
Figure 15 (CDCl₃). Compound (42).
B-Figure 16 (CDCl₃). Compound (43).
B—Figure 17 (CDCl₃). Compound (45).
Figure 18 (CDCl$_3$). Compound (46).
Figure 19. (CDCl₃). Compound (47).
B-Figure 20 (CDCl₃). Compound (48).
B-Figure 21a (CDCl₃). Compound (54a).
B-Figure 2lb (CDCl₃). Compound (54b).
B-Figure 22 (CDCl₃). Compound (55).
B-Figure 23 (CDCl₃). Compound (56).
B-Figure 24 (CDCl₃). Compound (57).
Figure 25 (CDCl₃). Compound (58).
B-Figure 26 (CDCl₃). Compound (50).
B-Figure 27 (CDCl₃). Compound (59).
B-Figure 28 (CDCl₃). Compound (60).
Figure 29 (CDCl₃). Compound (69).
B-Figure 30 (CDCl₃). Compound (70).
Figure 31 (CDCl₃) Compound (71).
Figure 32a (d$_6$-DMSO). NMR Tube reaction mixture at start. Compounds (50) and (64).
B-Figure 32b (d₆-DMSO). NMR tube reaction after 19 hr. Compound (65).
B-Figure 33a (d₆-DMSO). NMR tube reaction mixture at start. Compounds (50) and (71).
B-Figure 33b (d_6-DMSO). NMR tube reaction after 4 hr. Compound (72).
APPENDIX C

BROMINATION OF 1-ALKYL-2-PYRIDONES
WITH N-BROMOSUCCINIMIDE
Bromination of 1-Alkyl-3-methyl-2-pyridones with N-Bromosuccinimide

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The functionalization of a 3-methyl group attached to a pyridine or quinoline ring has proven to be an important step in several approaches to the synthesis of camptothecin and bromination with N-bromosuccinimide (NBS) met with only limited success. With the pyridine derivatives no bromination of the ring or alkyl substituent occurred unless the basicity of the nitrogen was decreased by an electronegative, α substituent. With 6-methyl- or 4,6-dimethyl-2-pyridone (1 or 2) NBS caused ring bromination to 3 and 4 rather than substitution of the methyl groups even using benzoyl peroxide as catalyst. The earlier report that 1,3-dimethyl-2-pyridone (5) gave bromination of the 3-methyl group with NBS to give 6 was recently questioned, for ring bromination to give 7 was confirmed as the product from this reaction.

Since 1-substituted 3-bromomethyl-2-pyridone would be a convenient intermediate the NBS reaction with 1-alkyl-3-methyl-2-pyridones (5 and 8) was reinvestigated. A dilute solution of 1-benzyl-3-methyl-2-pyridone (8) was treated with NBS and dibenzoyl peroxide in refluxing carbon tetrachloride for 50 min and a solid product remained after filtration and evaporation of the solvent. The NMR spectrum of the crude product was recrystallized twice from petroleum ether (bp 30-60 °C) and a product was obtained after vacuum distillation at 63 °C (0.05 mm)

**Experimental Section**

1-Benzyl-3-methyl-2-pyridone (8). To a solution of 6.44 g of 87% KOH in 150 ml of absolute ethanol at 50 °C was added 3-methyl-2-pyridine. The resulting solution was stirred for 20 min before the dropwise addition of benzyl chloride. The mixture was stirred at 50 °C for 3 h, concentrated under reduced pressure, poured into 180 ml of water, and extracted with chloroform (3 x 50 ml). The organic phase was washed with water and saturated salt solution, dried (MgSO₄), filtered, and concentrated to yield a light yellow oil which crystallized under pentane with cooling. The solid was collected and dried to give 15.75 g (86%) of 8 as white crystals, mp 69-71 °C. The product was recrystallized from petroleum ether (bp 30-60 °C)-methylene chloride to afford an analytical sample of 8: mp 70.5-71.5 °C; NMR (CDCl₃) δ 7.12-7.48 (m, including s at 7.36, 7 H total), 6.06 (t, 1 H), 5.15 (s, 2 H), 2.16 (s, 3 H); ir (KBr) 1645 cm⁻¹. Anal. Calcd for C₂₀H₂₃NO: C, 78.38; H, 6.58; N, 7.03. Found: C, 78.34; H, 6.78; N, 7.11.

1,3-Dimethyl-2-pyridone (5). Using the procedure above, 6.94 g (63.6 mmol) of 3-methyl-2-pyridine and 13.0 g (91.6 mmol) of methyl iodide gave after vacuum distillation 6.63 g (85%) of 5 as a clear oil: bp 63 °C (0.05 mm) [lit. bp 63-64 °C (1.6 mm)]; NMR (CDCl₃) δ 7.24-7.50 (m, 2 H), 6.16 (t, 1 H), 3.60 (s, 3 H), 2.16 (s, 3 H); ir (KBr) 1650 cm⁻¹.
1-Benzyl-5-bromo-3-methyl-2-pyridone (9). A solution of 1.0 g (5.02 mmol) of 8 in 10 ml of dry benzene was placed in a dry, nitrogen-filled flask. To the solution was added 0.90 g (5.02 mmol) of NBS and the mixture was heated at 90 °C for 50 min. The benzene was removed under reduced pressure, 25 ml of carbon tetrachloride was added to the residue, and the resulting mixture was filtered. The filter cake was washed with 25 ml of carbon tetrachloride and the filtrate was concentrated under reduced pressure leaving an orange oil as residue, the NMR of which showed less than 10% of 10. The oil crystallized on cooling, and trituration with 10 ml of anhydrous ether gave 0.95 g (68%) of crude 9 as a white solid, mp 86.5-89 °C. The solid was recrystallized twice from ether to give an analytical sample of 9: mp 96.5-97.5 °C; NMR (CDCl₃) δ 7.04-7.60 (m, including s at 7.23, 7 H total), 5.02 (s, 2 H), 2.12 (s, 3 H). Anal. Caled for C₁₃H₁₀BrNO: C, 41.68; H, 4.66; N, 6.83. Found: C, 41.68; H, 4.66; N, 6.83.

5-Bromo-1,3-dimethyl-2-pyridone (7). A solution of 0.83 g (6.7 mmol) of 3 in 12 ml of dry carbon tetrachloride was placed in a dry nitrogen-filled flask. To the solution was added 1.18 g (6.6 mmol) of purified NBS and the mixture was heated under reflux for 50 min. After this time 25 ml of carbon tetrachloride was added; the mixture was cooled and filtered; and the solvent was removed to afford 1.28 g (96%) of 7 as a light-yellow solid, mp 98-101 °C. Recrystallization of the product from petroleum ether (bp 30-60 °C) gave a fluffy white crystals: mp 105-106 °C (lit. mp 106-107 °C); NMR (CDCl₃) δ 7.30-7.55 (m, 2 H), 3.61 (s, 3 H), 2.20 (s, 3 H). Anal. Caled for C₆H₆BrNO: C, 41.61; H, 3.99; N, 6.93. Found: C, 41.68; H, 4.06; N, 6.83.

Acknowledgment. The authors wish to express appreciation to the National Cancer Institute of the National Institutes of Health for partial support of this research by Grant CA 12149. One of the authors (D.L.C.) also expresses appreciation to the Graduate School of the University of New Hampshire for summer fellowships which provided partial support for this research.

Registry No.—5, 6456-92-4; 6, 58802-10-1; 7, 51417-13-1; 8, 58802-11-2; 9, 58802-12-3; 10, 58802-13-4; 3-methyl-2-pyridone, 1003-56-1; benzyl chloride, 100-44-7; methyl iodide, 74-87-3; N-bromosuccinimide, 128-08-5.

References and Notes
(9) The NBS was purified by recrystallization from ten times its weight of water and drying under vacuum overnight (mp 182.5-184 °C).
(10) The residue contained less than 10% of compounds 5 and 7, combined, by NMR.
(11) The product contained only a trace (<2%) of compounds 5 and 6 by NMR.
(12) The manner and the time of heating after 50 min is not critical.
APPENDIX D

REGIOSELECTIVE NUCLEOPHILIC ADDITION TO 3,4-LUTIDINE
Regioselective Nucleophilic Addition to 3,4-Lutidine

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The usual orientation of nucleophilic addition at the 2 position of a 3-alkylpyridine can be changed by increasing the steric requirements of the nitrogen substituent. Thus the addition of phenylmagnesium bromide to the alkyl chloroformate ester salts of 3,4-lutidine is regioselective giving up to 90% addition of the aryl group at the 6 position. The large steric requirements of the 1-phenoxy carbonyl group or an ortho-substituted phenyl Grignard reagent gave 95% or greater regioselectivity of reaction at the less hindered α position of the 3,4-lutidine salt.

The reactions of nucleophiles with pyridines and pyridine derivatives may occur by addition at the 2, 4, or 6 position of the ring. When the nucleophile is an organometallic reagent the addition usually takes place adjacent to the nitrogen, at the 2 or 6 positions, and with the unsymmetrical ring having a 3-alkyl group, the addition is primarily at the 2 position.
Thus the reactions of phenyllithium with 3-picoline,\(^3\) 3-alkyl-1-ethoxypyrindinium bromides with Grignard reagents,\(^4\) and 3,4-lutidine methiodide with benzylmagnesium chloride\(^{3a,5}\) all gave the sole or major product compounds resulting from addition of the organometallic reagent at the 2 position. This unexpected regiospecificity has been rationalized as resulting from an "ortho" effect of the 3-alkyl group probably related to London forces.\(^3\)

The requirement for a series of 2-aryl-4,5-lutidines for a synthetic problem in this laboratory would be facilitated if the regiospecificity of the addition of an organometallic reagent to a 3,4-lutidine derivative could be controlled to give predominantly reaction at the less hindered, 6 position. To make use of this steric factor to govern the regiospecificity of the nucleophilic addition it was evident from the literature that a group with large steric requirements would have to be introduced on the nitrogen. Since the pyridines were the desired product, the nitrogen substituent must be easily lost in the aromatization of the intermediate dihydropyridine. The activation of the pyridine ring to reaction with a Grignard reagent by salt formation with a chloroformate, recently reported by Fraenkel and co-workers\(^6\) with 4-substituted pyridines, seemed to provide a possible method for controlling the regiospecificity.

The steric requirements of the nitrogen substituent were varied by changing the nature of the alkyl group of the ester of the chloroformate, and the various 1-alkoxy carbonyl-3,4-lutidinium salts (1) were treated with an aryl Grignard reagent. The NMR spectrum of the mixture of 1-alkoxycarbonyl-2-aryl-1,2-dihydro-3,4-lutidine (3) and 1-alkoxycarbonyl-2-aryl-1,2-dihydro-4,5-lutidine (2) was not resolved sufficiently to allow analysis of the product. Thus aromatization of the mixture by heating with sulfur gave the pyridines 4 and 5 which could be analyzed by the NMR. The results of the study are given in Table I.

### Results and Discussion

The reaction of 3,4-lutidine with the chloroformates gave the salts which in turn were treated with a Grignard reagent to give a mixture of dihydropyridines (2 and 3). Except for the product from the reaction of \(p\)-chlorophenylmagnesium bromide and the phenyl chloroformate salt of 3,4-lutidine, which was largely the solid 1-phenoxycarbonyl-2-p-chlorophenyl-4,5-dimethyl-1,2-dihydropyridine (2f), the oily mixtures of dihydropyridines were not analyzed. The products were aromatized by heating with sulfur rather than by reaction with \(n\)-butyllithium, the procedure previously described,\(^6\) since the former procedure is more convenient for preparative scale reactions.

The reactions of unhindered aryl Grignard reagents with the lutidine salts from ethyl and isobutyl chloroformate, alkyl groups with no branching near the carbonyl group, gave significant amounts of reaction at the 2 position than did other derivatives of 3,4-lutidine or the base itself. An increase in the steric requirements of the ester (1c,d,f) or in the Grignard reagent (g) gave much greater regioselectivity with nearly exclusive reaction at the 6 position. Thus with the hindered Grignard reagent, \(o\)-tolylmagnesium bromide, even the smallest ester, ethoxycarbonyl-lutidinium salts, gave nearly exclusively a single isomer. This orientation is particularly noteworthy when compared with the reaction of \(o\)-tolyl lithium or \(o\)-ethylphenyllithium with 3-picoline which was reported to give about 95% addition at the 2 position.\(^7\) Similar high regiospecificity was achieved with any aryl Grignard reagent with the phenyl chloroformate salt of 3,4-lutidine.

These results clearly show that orientation of nucleophilic arylation of 3-alkylpyridines can be controlled to give substitution at the position ortho to the alkyl group using the base or by using our procedure to give substitution “para” to the alkyl substituent.

### Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus or a Mel-Temp apparatus and were not corrected for thermometer stem exposure. Elemental analyses were determined using an F and M Model 185 C, H, and N analyzer. Infrared spectra were determined using Perkin-Elmer Model 137 or 337 spectrometers with samples prepared as mulls or KBr pellets. The nuclear magnetic resonance spectra were determined using a JEOL Model MH-100 spectrometer.

### Table I

<table>
<thead>
<tr>
<th>Compd</th>
<th>R'</th>
<th>Ar</th>
<th>Overall yield, %</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH(_2)CH(_3)</td>
<td>C(_6)H(_5)</td>
<td>78/22</td>
<td>Ether</td>
</tr>
<tr>
<td>b</td>
<td>i-C(_3)H(_7)</td>
<td>C(_6)H(_5)</td>
<td>75/25</td>
<td>THF</td>
</tr>
<tr>
<td>c</td>
<td>i-C(_3)H(_7)</td>
<td>C(_6)H(_5)</td>
<td>90/10</td>
<td>Ether</td>
</tr>
<tr>
<td>d</td>
<td>CH(_3)CH(_2)</td>
<td>p-C(_6)Cl(_2)</td>
<td>92/6</td>
<td>THF</td>
</tr>
<tr>
<td>e</td>
<td>CH(_3)CH(_2)</td>
<td>p-C(_6)Cl(_2)</td>
<td>62/38</td>
<td>THF</td>
</tr>
<tr>
<td>f</td>
<td>CH(_3)</td>
<td>o-CH(_3)C(_6)H(_3)</td>
<td>95/5</td>
<td>THF</td>
</tr>
<tr>
<td>g</td>
<td>CH(_3)CH(_2)</td>
<td>o-CH(_3)C(_6)H(_3)</td>
<td>95/5</td>
<td>THF</td>
</tr>
<tr>
<td>h</td>
<td>CH(_3)</td>
<td>o-CH(_3)C(_6)H(_3)</td>
<td>&gt;95(^a)</td>
<td>THF</td>
</tr>
</tbody>
</table>

\(^a\)Only a trace of 5 could be detected in the NMR spectrum.
2.16 (s, N M R (CDC\textsubscript{L}) 203-204 °C [lit. of 4f as a light yellow oil; b p 117-120 °C (0.35 mm); picrate m p 202-203 °C; NMR (CDC\textsubscript{L}) δ 8.58 (s, 1 H), 8.18-8.28 (m, 2 H), 7.44-7.70 (m, 4 H), 2.16 (s, 6 H).]

2-p-Chlorophenyl-4,5-dimethylpyridine (4f). A mixture of 15.0 g (44.14 mmol) of crude 2f and 1.27 g (39.73 mmol) of sublimed sulfur was heated with stirring at 190-200 °C for 45 min. The reaction mixture was cooled, dissolved in 150 ml of ether, and placed over sodium hydroxide pellets overnight. The solution was filtered and washed with 50 ml of 20% sodium hydroxide solution and 50 ml of water. The solution was extracted with three 50-ml portions of 10% hydrochloric acid. The acid extracts were filtered, washed with 25 ml of ether, made basic with 20% sodium hydroxide, and extracted with four 50-ml portions of ether. The ether extracts were washed with four 50-ml portions of ether. The organic layer was washed with ether and dried (K\textsubscript{2}CO\textsubscript{3}). 71.71; H, 7.65; N, 6.56. 

2-(o-Tolyl)-4,5-dimethylpyridine (4g). Using the procedure for the preparation of 4f, 10.71 g (0.1 mol) of 3,4-lutidine, 11.19 g (0.1 mol) of ethyl chloroformate, and 0.12 mol of o-tolylmagnesium bromide in 100 ml of THF gave, after vacuum distillation, 16.2 g of a yellow oil. Treatment with 1.91 g (59.7 mmol) of sublimed sulfur gave, after vacuum distillation, 9.0 g (49%) of a yellow oil. The oil was treated with Norite-chloroform and redistilled to give an analytical sample of 4g: bp 110-115 °C (0.35 mm); picrate, mp 166-167 °C; NMR (CDC\textsubscript{L}) δ 8.64 (s, 1 H), 7.35-7.68 (m, 4 H), 7.30 (s, 1 H), 2.43 (s, 3 H), 2.24 (s, 6 H).

Anal. Calc'd for C\textsubscript{13}H\textsubscript{15}ClN: C, 85.24; H, 7.66; N, 7.10. Found: C, 85.28; H, 7.65; N, 7.12.

Acknowledgment. The authors wish to express appreciation to the National Cancer Institute of the NIH for partial support of this project from Grant CA-12149. One author, D.L.C., further expresses appreciation to the Graduate School of the University of New Hampshire for a Summer Fellowship for Graduate Teaching Assistants. The authors also wish to thank Reilly Tar and Chemical for a generous supply of 3,4-lutidine.

Registry No.—2f, 59463-69-3; 4d, 27063-84-9; 4f, 27063-85-0; 4g, 59463-71-7; 3,4-lutidine, 583-58-4; phenyl chloroformate, 188-14-8; p-chlorophenyl bromide, 106-39-8; phenyl bromide, 108-86-1; o-tolyl bromide, 95-46-5; ethyl chloroformate, 541-41-3.

References and Notes
(5) (a) Reference 3b, p 304; (b) M. Alveer, J. Bosch, and J. Canak, An. Quim., 71, 807 (1975).