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REPORT NUMBER 11

SYNTHESIS OF RATIONALLY DESIGNED ORGANIC COMPOUNDS FOR MALARIA CHEMOTHERAPY STUDIES

ANNUAL PROGRESS REPORT

by

C. C. Cheng, Ph.D.
Ping-Lu Chien, Ph.D.

14 October 1976

(For the period 1 August 1975 to 31 July 1976)

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Midwest Research Institute
Kansas City, Missouri 64110

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

During the present report period, 20 compounds of the following categories have been synthesized, characterized, and submitted for antimalarial evaluation: (a) compounds having a triangular structural feature common to many causal prophylactic antimalarial agents, and (b) deazafebrifugine and related compounds. 8-(6-Amino-4-heptylamino)-6-methoxy-4-methylquinoline diphosphate exhibited good antimalarial activity against P. berghei.

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ABSTRACT

During the present report period, 20 compounds of the following categories have been synthesized, characterized, and submitted for antimalarial evaluation: (a) compounds having a triangular structural feature common to many causal prophylactic antimalarial agents, and (b) deazafebrifugine and related compounds.

8-(6-Amino-4-heptylamino)-6-methoxy-4-methylquinoline diphosphate (WR-226573, MO-535) exhibited good antimalarial activity against P. berghei in the WRAIR screening.

The outstanding antimalarial activity of 8-(6-amino-3-hexylamino)-6-methoxy-4-methylquinoline diphosphate (WR-215761, MO-485) against P. berghei was reported last time. During this report period, WR-215761 was also found to display excellent prophylactic antimalarial activity in Schmidt's SR screening.

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FOREWORD

This annual report was prepared at Midwest Research Institute under Contract No. DAMD-17-76-C-6015 with the U.S. Army Medical Research and Development Command.

The period of research covered in this report is from 1 August 1975 to 31 July 1976. The work was carried out under the direction of Dr. C. C. Cheng, Principal Investigator. The synthetic work was performed by Dr. Ping-Lu Chien, Mr. William H. Burton (part-time) and Dr. Shou-Jen Yan (part-time).

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I. INTRODUCTION

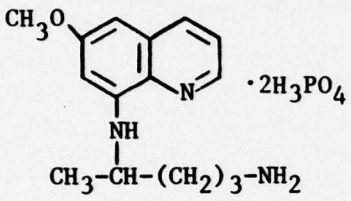
This is the Eleventh Annual Progress Report from Midwest Research Institute under Contract No. DAMD-17-76-C-6015 with the U.S. Army Medical Research and Development Command on preparation of organic compounds as potential antimalarial drugs.

During the present report period, we have studied the synthesis and characterization of compounds of the following categories: (a) compounds having a triangular structural feature common to many causal prophylactic antimalarial agents, and (b) deazafebrifugine and related compounds. A total of 20 compounds have been synthesized, characterized, and submitted for antimalarial evaluation.

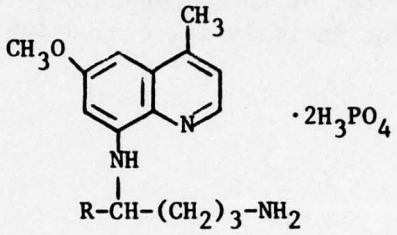
II. RESULTS AND DISCUSSION

A. Compounds Containing a Common Triangular Causal Prophylactic Antimalarial Structural Feature

The undesired toxicity exhibited by the prophylactic drug primaquine (A-1) prompted a structural modification study of 8-aminoquinolines. In our laboratory, attention has been focused to the side chain modification. Consequently, 8-(6-amino-3-hexylamino)-6-methoxy-4-methylquinoline diphosphate (A-2a) was synthesized and was found to possess outstanding activity against *P. berghei* with no toxicity to the host animals even at 640 mg/kg.[1]



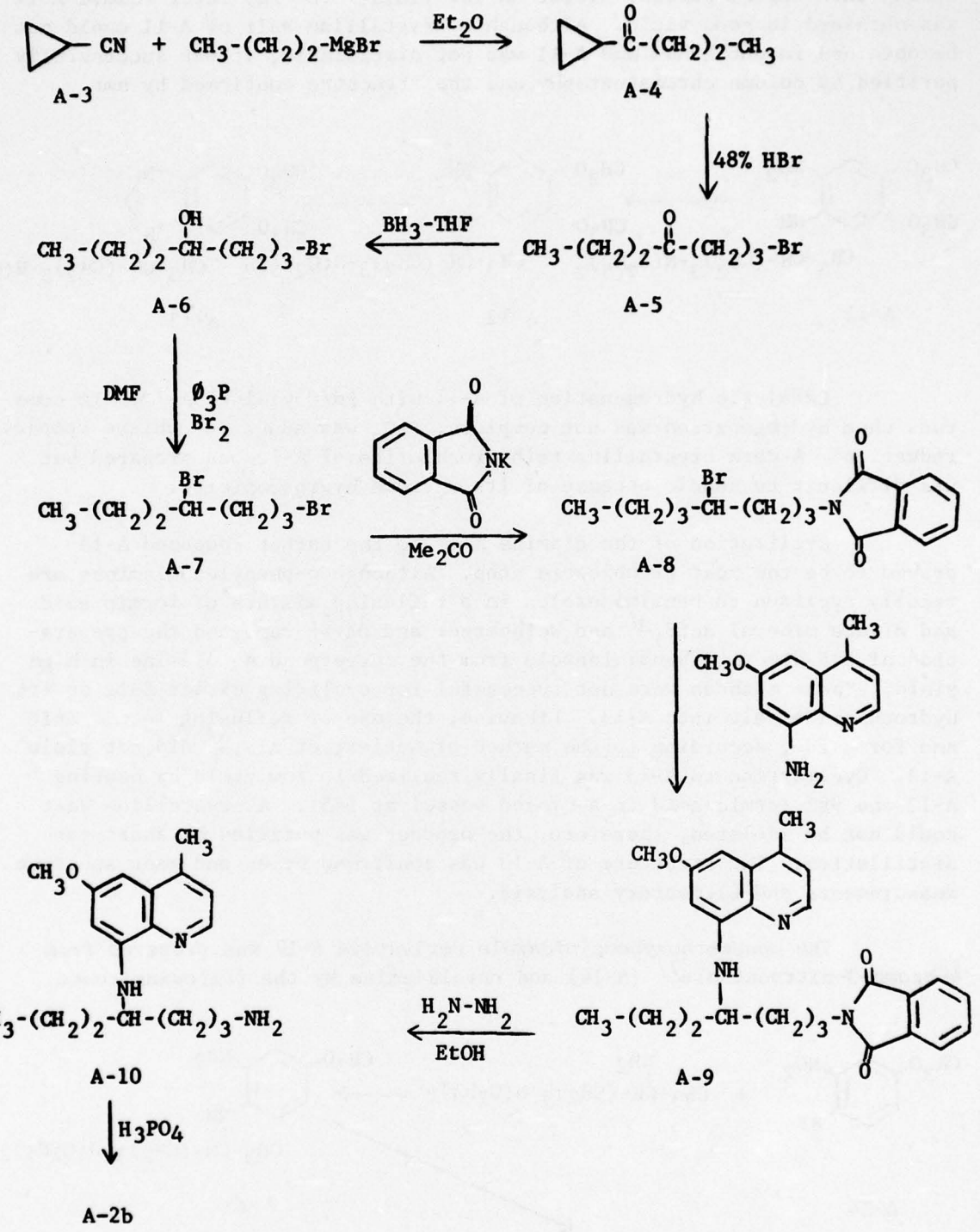
A-1



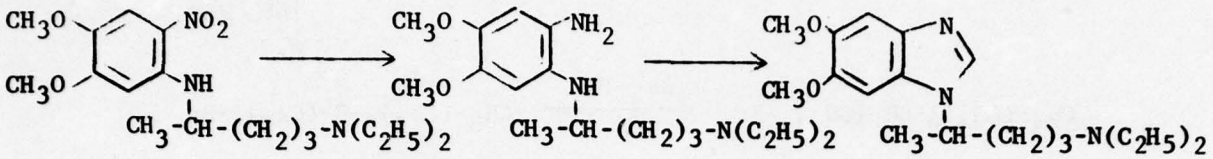
A-2a. R = CH_2-CH_3
b. R = $(CH_2)_2$-CH_3

During the present progress report period, a higher homolog of A-2a, 8-(1-amino-4-heptylamino)-6-methoxy-4-methylquinoline diphosphate (A-2b) was synthesized and submitted. All these compounds conform to a triangular structural feature common to many causal prophylactic antimalarial agents.[2]

1-Cyclopropylbutan-1-one (A-4) was prepared according to the method of Bruylants,[3] with some modification, from cyclopropyl cyanide (A-3) and propylmagnesium bromide. Treatment of A-4 with 48% HBr at room temperature for 20 hr yielded 1-bromoheptan-4-one (A-5). The latter was reduced to 1-bromo-4-hydroxyheptane (A-6) with diborane in THF. Compound A-6 was converted to 1,4-dibromoheptane (A-7) by triphenylphosphine dibromide in DMF, which gave N-(4-bromoheptyl)phthalimide (A-8) upon refluxing with a mixture of potassium phthalimide and acetone. Compound A-8 was heated with 8-amino-6-methoxy-4-methylquinoline and diisopropylamine in a steel vessel at 160° for 36 hr to yield 6-methoxy-4-methyl-8-(1-phthalimido-4-heptylamino)-quinoline (A-9), which was treated with hydrazine to form the free base A-10. The latter was then treated with excess phosphoric acid to give the desired target compound A-2b.


A-3
A-4
A-5
A-6
A-7
A-8
A-9
A-10
A-2b
48% HBr
BH3-THF
DMF
Ø3P
Br2
Me2CO
H2N-NH2
EtOH
H3PO4

The dimethoxybenzimidazole target compound A-13 was also synthesized during this report period, albeit in low yield. The key intermediate A-11 was obtained in good yield. Although a crystalline salt of A-11 could not be obtained in our hands and A-11 was not distillable, it was successfully purified by column chromatography and the structure confirmed by nmr.

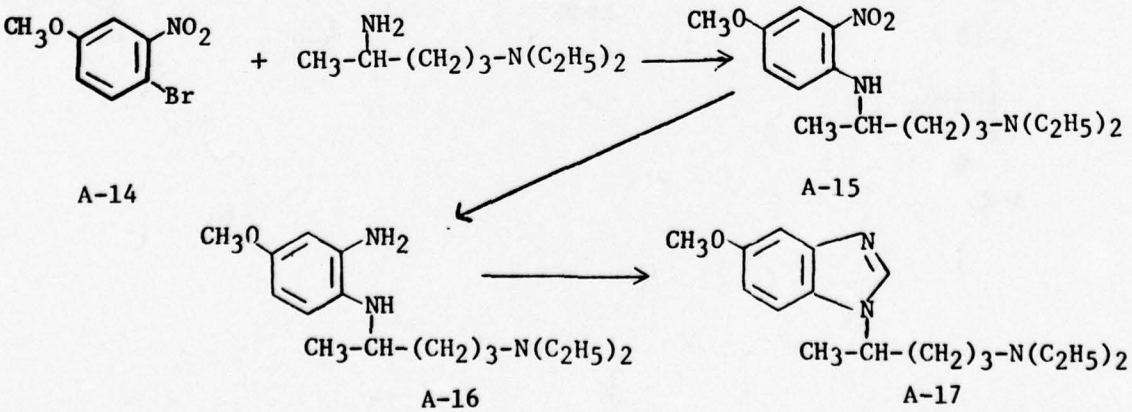


A-11 A-12 A-13

Catalytic hydrogenation of A-11 with Pd/C yielded A-12. In some runs when hydrogenation was not complete, PtO_2 was added to achieve complete reduction. A dark crystalline trihydrochloride of A-12 was prepared but was difficult to handle because of its extreme hygroscopicity.

Cyclization of the diamine A-12 to the target compound A-13 proved to be the most troublesome step. Although o-phenylenediamines are readily cyclized to benzimidazoles in a refluxing mixture of formic acid and dilute mineral acid;[4] and Weinberger and Day[5] reported the preparation of 5,6-dimethoxybenzimidazole from the corresponding diamine in high yield. These methods were not successful for cyclizing either A-12 or its hydrochloride salt into A-13. Likewise, the use of refluxing formic acid and formamide, according to the method of Getler, et al.,[6] did not yield A-13. Cyclization to A-13 was finally realized in low yield by heating A-12 and 98% formic acid in a closed vessel at 165°. A crystalline salt could not be isolated, therefore, the product was purified by short-path distillation. The structure of A-13 was confirmed by uv and mass spectrum measurements and elementary analysis.

The monomethoxybenzimidazole derivative A-17 was prepared from 4-bromo-3-nitroanisole[7] (A-14) and novoldiamine by the following route.

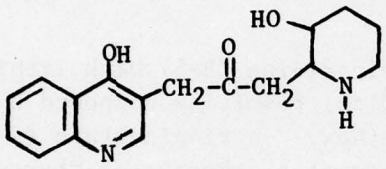


A-14 A-15 A-16 A-17

A number of experiments were conducted in order to obtain a good yield of A-15, including the use of pyridine as solvent and copper as catalyst. The best yield (22%) was obtained when sodium bicarbonate was added to the reaction mixture. Subsequent catalytic reduction of A-15 to A-16 and the cyclization to the target compound A-17 with 98% formic acid in a closed vessel at 165° was accomplished in an overall yield of 74%. As with the dimethoxy analog, a crystalline salt could not be obtained in our hands. Compound A-17 was, therefore, purified by short-path distillation.

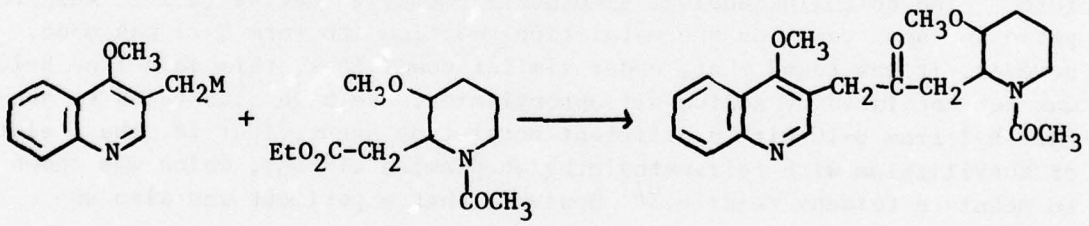
B. 3-Deazafebrifugine and Related Compounds

Following routes have been studied for the synthesis of 3-deazafugine (B-1).



B-1

1. Condensation between the metalated 4-Methoxy-3-methylquinoline (B-2) and Ethyl 1-Acetyl-3-methoxy-2-piperidylacetate (B-3)



B-2
(M = Na or Li)

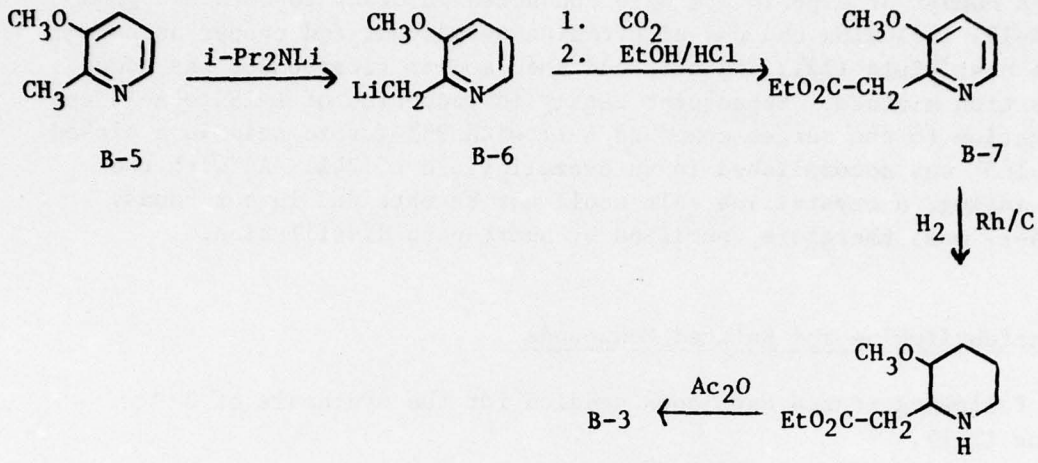
B-3

B-4

↓

B-1

Compound B-3 was prepared by the following procedure.

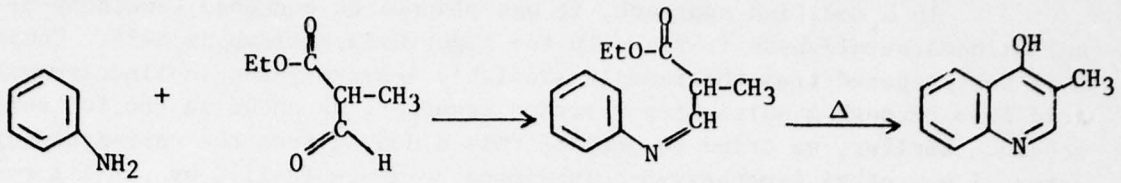


B-5 B-6 B-7 B-3

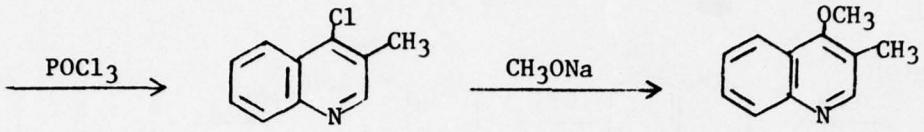
Lithiation of 3-methoxy-2-methylpyridine (B-5) with lithium diisopropylamide followed by treatment of the resulting compound B-6 with CO_2 gave after esterification, ethyl 3-methoxy-2-pyridylacetate (B-7). The latter was hydrogenated in the presence of 5% rhodium-on-charcoal and the resulting piperidine B-8 acetylated to give one of the desired reactants B-3.

Since the successful metalation of 3-picoline and its subsequent reaction with esters to produce 3-picolyl ketones was reported in the literature,[8] the quinoline analog, 4-methoxy-3-methylquinoline (B-10), was prepared and an attempt on the metalation reaction (to form B-2) was made. However, it was found that, under similar conditions, this quinoline B-10 was not metalated by sodium diisopropylamide. We have also tried to prepare B-2 from B-10 with a different metalating agent, that is, the chelate of butyllithium with tetramethylethylenediamine (TMEDA), which was shown to metalate toluene readily.[9] However, that experiment was also unsuccessful.

4-Methoxy-3-methylquinoline (B-10) was prepared by chlorination of 4-hydroxy-3-methylquinoline (B-9) followed by treatment with sodium methoxide. The quinolinol B-9 used in this experiment was obtained in low overall yield from aniline and ethyl formylpropionate. This compound could be made in better yield by Steck's method[10] from the corresponding diester followed by decarboxylation. Initial lithiation attempts of B-10, however, were not successful.

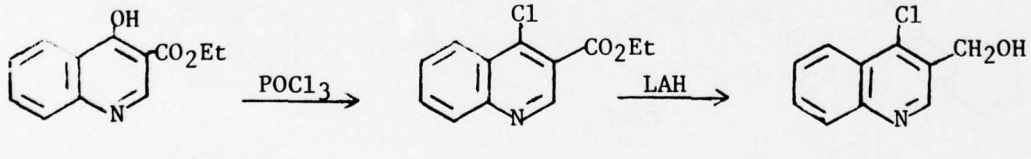


B-9

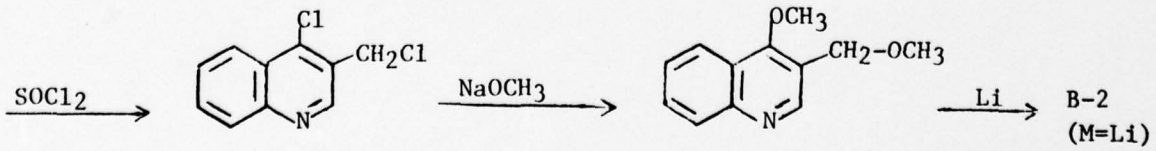


B-10

As an alternative, 4-methoxy-3-methoxymethylquinoline (B-15) is being prepared from 4-chloro-3-quinolinemethanol (B-13). It is anticipated that the ether B-15 should react with lithium metal to form the desired lithio compound B-2 by analogy with benzyl methyl ether. The latter was shown to react readily with lithium to produce benzyllithium in good yield.[11] 4-Chloro-3-quinolinemethanol (B-13) has been prepared by lithium aluminum hydride reduction of 4-chloro-3-carbethoxyquinoline[1] (B-12) at low temperature.[12] (For comparison, previous attempts on reduction of 4-methoxy-3-carbethoxyquinoline with lithium aluminum hydride were unsuccessful, while Red-Al apparently over-reduced this compound to a quite complex mixture of products, even at a reaction temperature of -70°.) However, under comparable reaction conditions, compound B-15 did not appear to react with lithium to any extent. The chloromethyl derivative B-14 also failed to give the desired lithio compound when treated with butyllithium at low temperature.

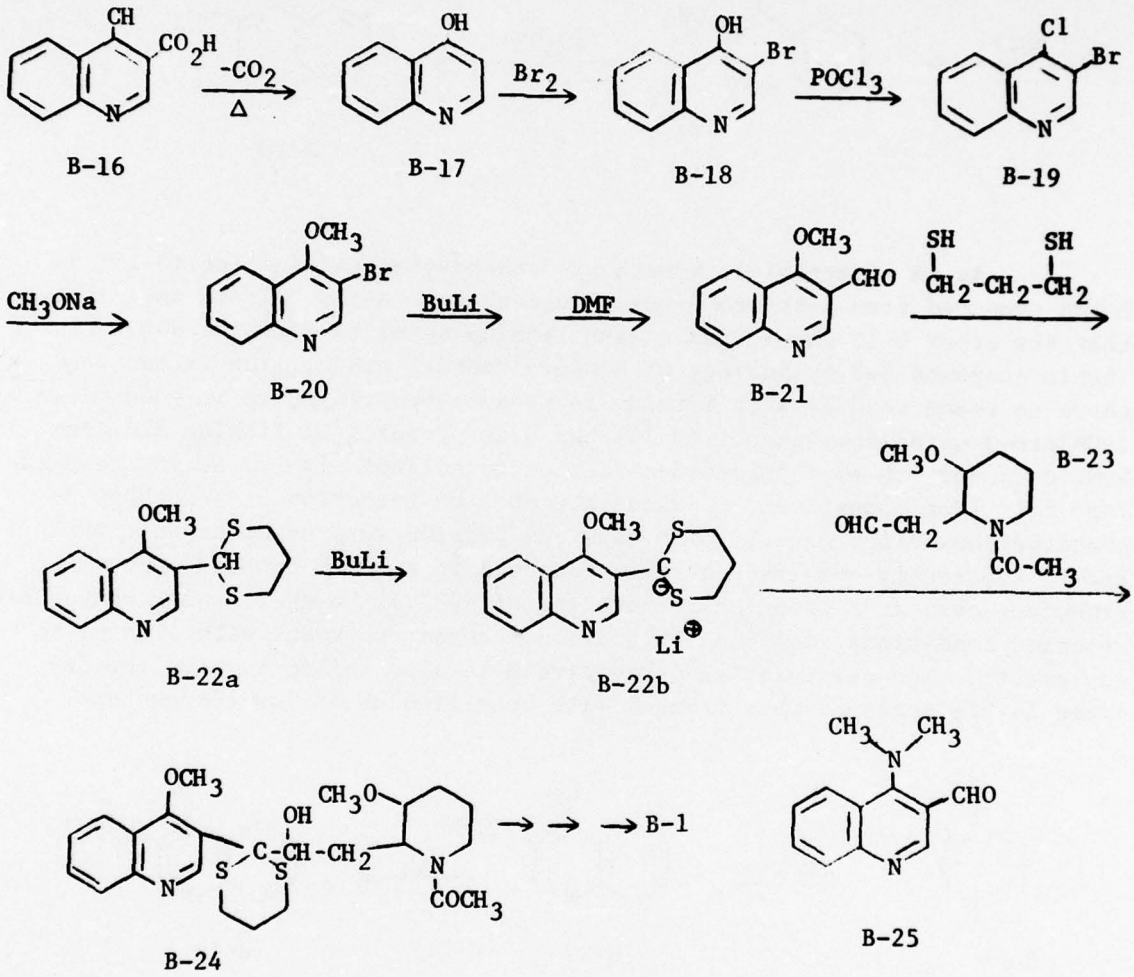


B-11 B-12 B-13



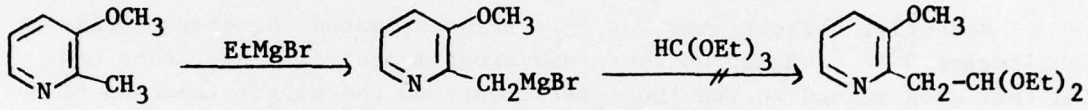
B-14 B-15 B-2 (M=Li)

In a modified approach, it was planned to condense 4-methoxy-3-quinolinecarboxaldehyde (B-21) with the piperidylacetaldehyde B-24. Compound B-21 was prepared from the readily available 4-hydroxy-3-quinolinecarboxylic acid B-16 through a multi-step reaction sequence, as shown in the following scheme. Earlier, we tried to prepare this aldehyde from the corresponding ester, i.e., ethyl 4-methoxy-3-quinolinecarboxylate (B-11), by partial reduction with Red-Al or diisobutylaluminum hydride, or by the McFadyen-Stevens method,[13] but were unsuccessful.



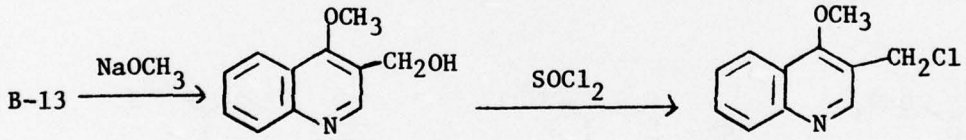
According to the original plan, the aldehyde B-21, which may be obtained by reduction from the corresponding ester B-3, is to be converted into a dithiolane derivative B-22a, from which the anion B-22b may be readily generated by the action of butyllithium. This anion should react with the piperidylacetaldehyde B-23 to give the adduct B-24, which, upon desulfurization, oxidation and hydrolysis, could lead to the target compound B-1. However, although a small quantity of the aldehyde B-21 could be obtained by treatment of 3-bromo-4-methoxyquinoline (B-20) with butyllithium followed by dimethylformamide, attempted preparation of larger quantity of B-21 yielded a different product. It was identified by NMR and elemental analysis to be 4-dimethylamino-3-quinolinecarboxaldehyde (B-25).

Another synthetic method involving the reaction of the Grignard compound B-27 with triethyl orthoformate[14] was explored, but the desired intermediate B-28 was not obtained. Because of the failure to prepare the required aldehyde B-21, this approach is not being pursued.



B-26 B-27 B-28

The failure of aldehyde condensation approach prompted a reinvestigation of lithiation of 3-chloromethyl-4-methoxyquinoline [(B-30) prepared from 4-chloro-3-hydroxymethylquinoline (B-13) via the 4-methoxyl intermediate B-29], and of 4-methoxy-3-methylquinoline (B-10).



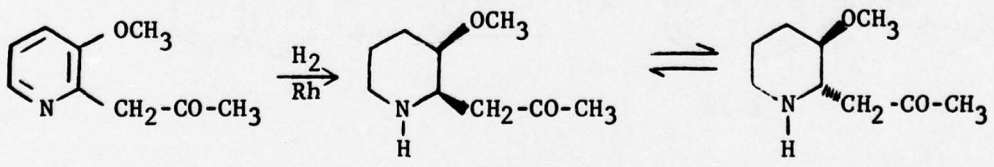
B-29 B-30

Lithiation attempts of B-30 were still unsuccessful. Lithiation of 4-methoxy-3-methylquinoline (B-10) was reinvestigated by employing deuterium oxide quenching technique. The BuLi-TMEDA chelate was again proved to be too reactive for this purpose. Even at -70°, a complex mixture of the reaction products was formed. Nevertheless, lithium diisopropylamide was found to be quite suitable for this reaction. By lowering the reaction temperature to -70°, clean lithiation of the 3-methyl group could be achieved without appreciable side reactions, as indicated by NMR.

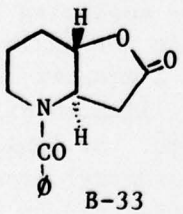
The lithio derivative B-2 (M=Li) thus obtained reacted smoothly with the 2-piperidylacetate B-3 as anticipated,[8] to give the intermediate B-4, which possessed the basic skeleton of the deazafebrifugine B-1. That the reaction of the lithio compound with the piperidylacetate B-3 stopped cleanly at the ketone stage is apparently due to the fact that as soon as the ketone B-3 was formed, it was immediately converted to its enolate salt under the reaction conditions. In work-up, the ketone can be isolated by extraction after the aqueous phase is neutralized. The structure of this intermediate was confirmed by spectral evidence (IR, NMR).

Deblocking of the protecting groups in the intermediate B-4 was carried out by two different methods: Heating of B-4 with 48% hydrobromic acid removed both the N- and O- protecting groups at the same time. Alternatively, the N-acetyl group could be hydrolyzed first by boiling with dilute hydrochloric acid and the remaining ether functions were cleaved by hydrobromic acid. However, repeated attempts to isolate the target compound as a solid or a crystalline hydrochloride or fumaric acid salt were, as yet, unsuccessful.

Recently, Berkelhammer, et al., reinvestigated the stereochemistry of febrifugine.[15,16] Based on their new experimental findings, they concluded that with regard to the two substituents on the piperidine ring of febrifugine, that portion of the molecule is actually of trans configuration, rather than cis, as originally assigned by Baker. The evidence presented by these workers consisted of: (1) the piperidylpropanone intermediate B-31 used in Baker's third synthesis[17] readily undergoes thermal isomerization to an equilibrium mixture of the ratio of 2-3:1 in favor of the trans isomer B-32. This facile isomerication has since been confirmed by us; (2) as shown by NMR analysis, the lactone B-33, a key intermediate of Baker's second synthesis actually has a trans ring junction instead of cis, as designated by Baker.[18]

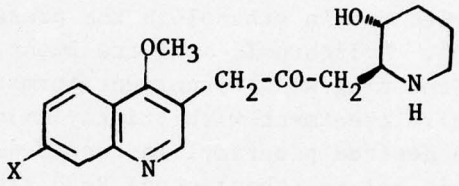


B-31 B-32

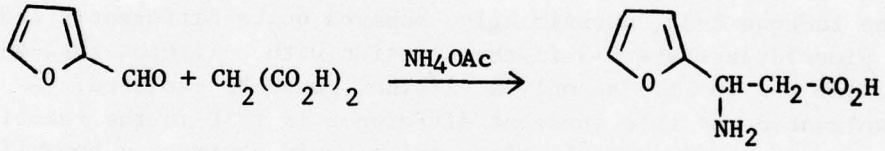


B-33

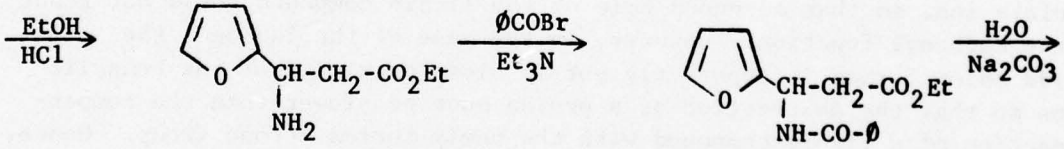
Since the piperidylacetate B-3 used in the present synthesis must be predominantly in the cis configuration, the final product obtained should also be mainly cis, the wrong isomer. In the febrifugine series, it is known that the cis isomer is usually more difficult to crystallize than the trans isomer. It is therefore reasonable to assume that the failure to obtain the final product as a solid or crystalline salt with hydrogen chloride or fumaric acid is due to predominance of the cis isomer in the crude product. In order to obtain the desired target compound with correct trans configuration, we then decided to synthesize the isomerically pure trans lactone B-33 and to use this in the place of the piperidylacetate B-3 in the reaction with the lithio compound B-2 (M=Li). The target compound prepared in this manner, having a fixed trans configuration, should be easier to solidify or crystallize after being converted to its hydrochloride or fumaric acid salt. In addition, this trans lactone will serve as the intermediate for the synthesis of the other series of the target compounds, that is, the 4-methyl ether analogs B-34.



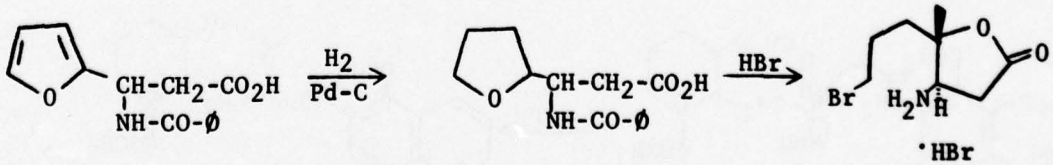
B-34 X = H, Cl



B-35



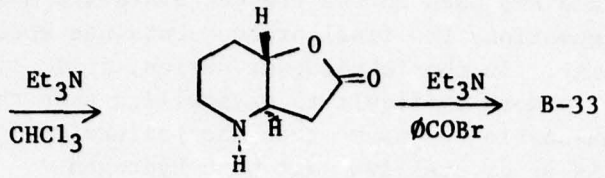
B-36 B-37



B-38 B-39

·HBr

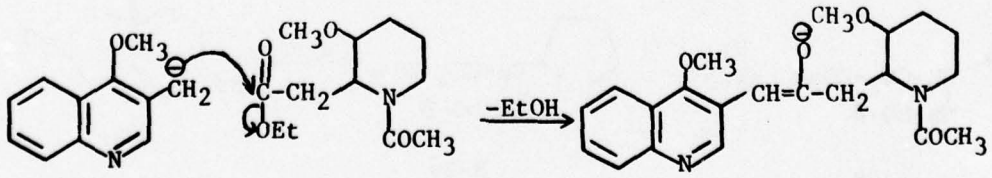
B-40

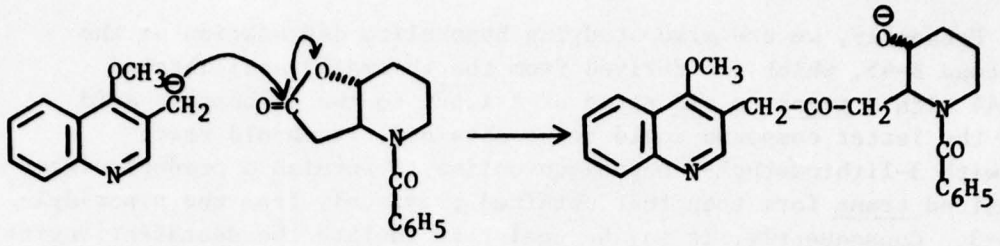


B-41

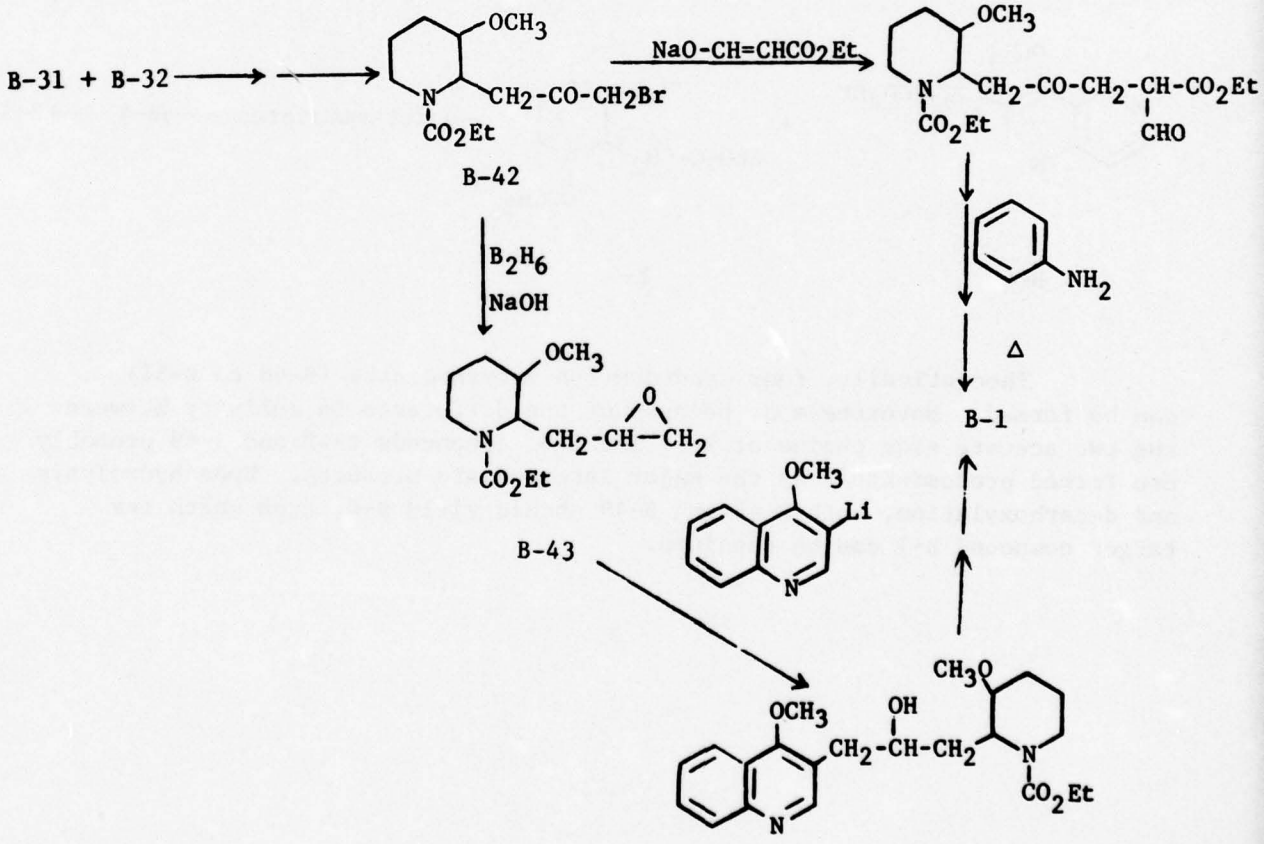
The synthesis of the trans lactone B-33 was carried out essentially by the method of Baker.[18] 3-Amino-3-(2-furyl)-propionic acid (B-35) was prepared by the reaction of furfural with malonic acid and ammonium acetate in ethanol. Direct benzoylation of the amino acid in aqueous base posed some difficulty. Later, the benzamido acid B-38 was made by a more circuitous method, but in more satisfactory yield, through the ethyl ester B-36. Surprisingly, the benzamido ester B-37 could not be readily hydrogenated so that it was hydrolyzed to the acid B-38. Catalytic reduction of compound B-38 could then be carried out in ethanol in the presence of palladium-on-charcoal catalyst at 50°. Hydrobromic acid treatment of the tetrahydrofuryl acid B-39 opened the ring with concurrent formation of the lactone B-40, which, on successive treatment with triethylamine and benzoyl bromide in chloroform, gave the desired piperidyl lactone B-41. After purification through a chromatographic column, the lactone B-33 finally crystallized and was purified by recrystallization. Its physical property and spectral data are in close agreement with those reported in the literature.[16,18]

The lactone B-33, surprisingly, behaved quite differently from that of the piperidylacetate B-3 in the reaction with 3-lithiomethyl-4-methoxyquinoline B-2 (M=Li), as only a carbinol could be isolated. A plausible explanation of this apparent difference is that in the reaction involving an ester, the incipient ethoxy anion could abstract a benzylic proton the instant the keto product is formed, resulting in the formation of an enolate ion, so that a second mole of the lithio compound could not react with the carbonyl function. However, in the case of the lactone, the alkoxide anion formed is apparently not in close proximity of the benzylic protons so that the abstraction of a proton must be slower than the competing reaction of a lithio compound with the newly formed ketone group. Hence, a carbinol is the sole product.

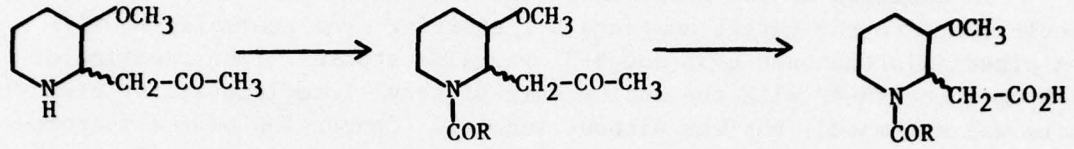




In addition to the general approach already described, a different synthetic route to the target compound B-1 starting from thermally equilibrated piperidylpropanones B-31 and B-32 was also studied. The reaction of the α-bromoketone B-42 with the sodium salt of ethyl formylacetate or diethyl malonate was attempted, but was without success. Conversion of the α-bromoketone B-42 to the epoxide B-43 could be carried out by treatment of the ketone with diborane followed by base (but not by the action of sodium borohydride). Since 3-lithio-4-methoxyquinoline (B-2, M=Li) probably could not be stable up to a temperature high enough to allow the reaction with the epoxide B-43 to proceed, this approach was not further investigated.

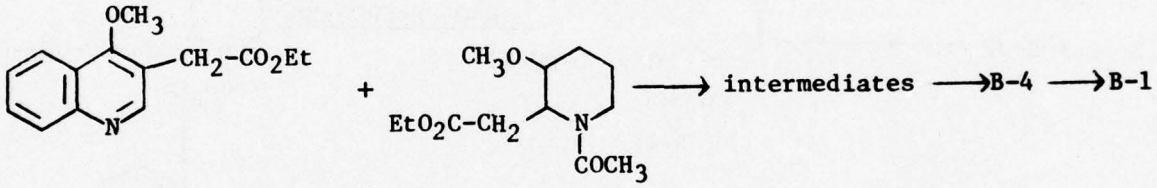


Presently, we are also studying hypohalite degradation of the methyl ketone B-45, which was derived from the thermally equilibrated ketone B-44 with a trans to cis ratio of 2:1,[15] to the carboxylic acid B-46. If the latter compound could be so obtained, it should react smoothly with 3-lithiomethyl-4-methoxyquinoline to furnish a product richer in the desired trans form than that obtained previously from the piperidyl-acetate B-3. Consequently, it may be easier to isolate the deazafebrifugine salt in a solid form.



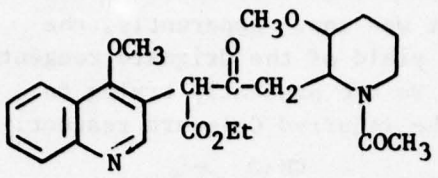
B-44 B-45 B-46

2. Condensation between Ethyl 4-Methoxy-3-quinolinylacetate (B-47) and Ethyl 1-Acetyl-3-methoxy-2-piperidylacetate (B-3):

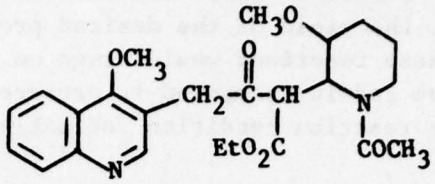


B-47 B-3

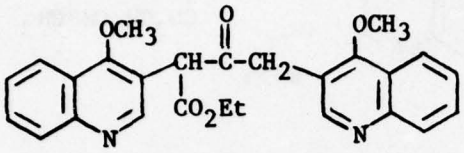
Theoretically, four condensation intermediates (B-48 to B-51) can be formed. Nevertheless, because of the difference in activity between the two acetate side chains of B-47 and B-3, compounds B-48 and B-49 probably are formed predominately as the major intermediate products. Upon hydrolysis and decarboxylation, both B-48 and B-49 should yield B-4, from which the target compound B-1 can be obtained.



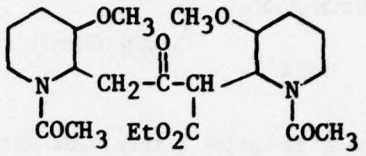
B-48



B-49

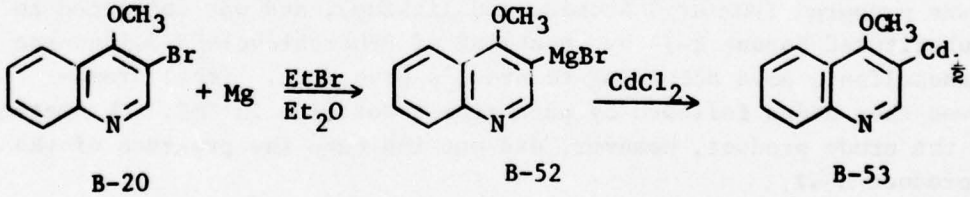


B-50

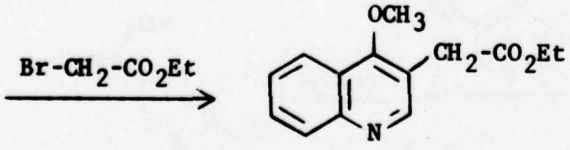


B-51

Compound B-3 has already been prepared, as discussed in the preceeding section. For the preparation of B-47, the following studies were conducted. Jones and Young[19] reported that arylcadmium compounds could react with α-halo esters or ketones to give α-aryl substituted esters or corresponding ketones. This reaction was therefore studied. Under normal conditions, 3-bromo-4-methoxyquinoline (B-20) did not form a Grignard reagent readily, but it did react with magnesium to a certain extent by using the entrainment method. However, the reaction could not always be carried to completion. When the quinolylcadmium compound B-53, prepared <u>in situ</u> from the incompletely formed Grignard compound, was allowed to react with ethyl bromoacetate, the desired quinolylacetate could not be obtained and most of the starting material was recovered.

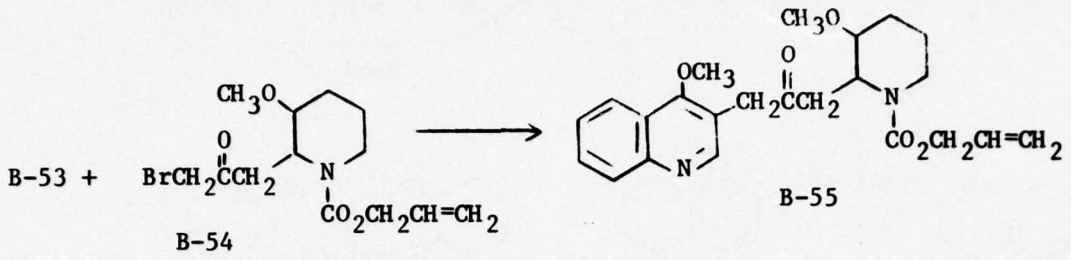


B-20 B-52 B-53

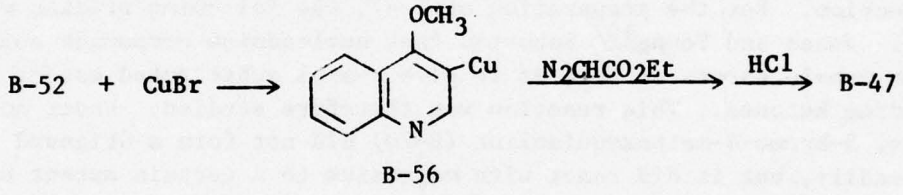


B-47

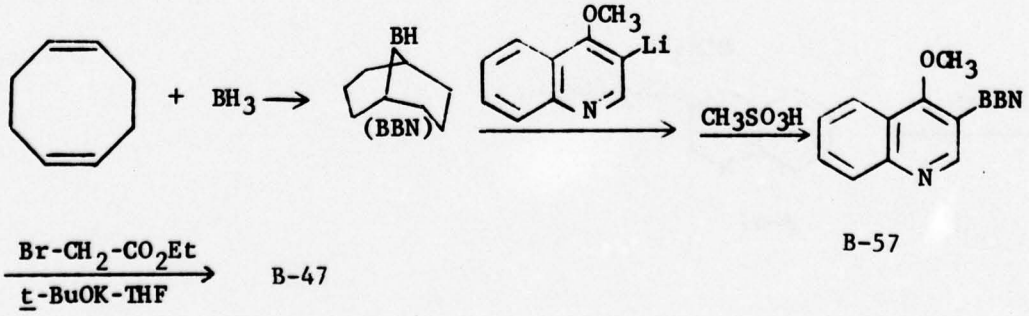
The reaction of the cadmium compound B-53 with the α-bromoketone B-54 was also studied. There was some indication that this reaction did proceed. But the yield of the desired product was low. Apparently, the success of these reactions would hinge on the yield of the Grignard reagent, from which the cadmium compound is prepared. We are presently trying to find a better reaction condition for making the required Grignard reagent.



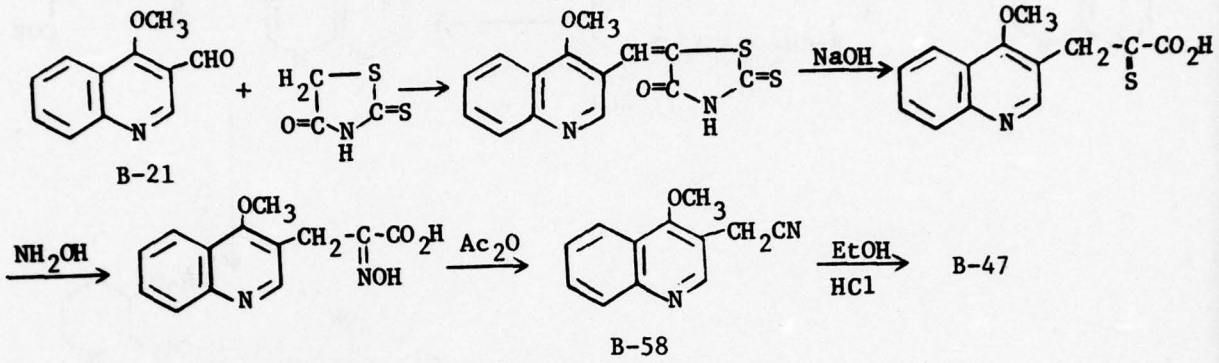
In a related study, an attempt was made to prepare the quinolylcopper compound B-56, which could then be treated with ethyl diazoacetate according to the method of Sato and Watanabe.[20] Probably due to incomplete formation of the Grignard reagent, the desired product was, again, not isolated.



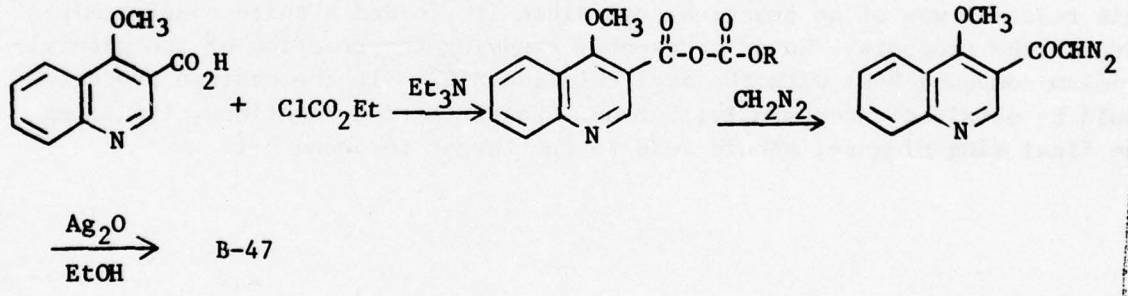
We also studied Brown's reaction of B-aryl-9-borabicyclo[3.3.1]-nonane with α-haloesters and ketones under the influence of potassium t-butoxide[21] for the preparation of the quinolylacetate B-47. 3-Lithio-4-methoxyquinoline was prepared in the usual manner from the 3-bromoquinoline B-20 by the action of butyllithium at -70° (in Brown's work the aryllithium was prepared from aryl bromide and lithium), and was converted to the trisubstituted borane B-57 by treatment of 9-borabicyclo[3.3.1]nonane and methanesulfonic acid according to Brown's procedure. Ethyl bromoacetate was then added followed by potassium t-butoxide in THF. Chromatography of the crude product, however, did not indicate the presence of the desired product B-47.



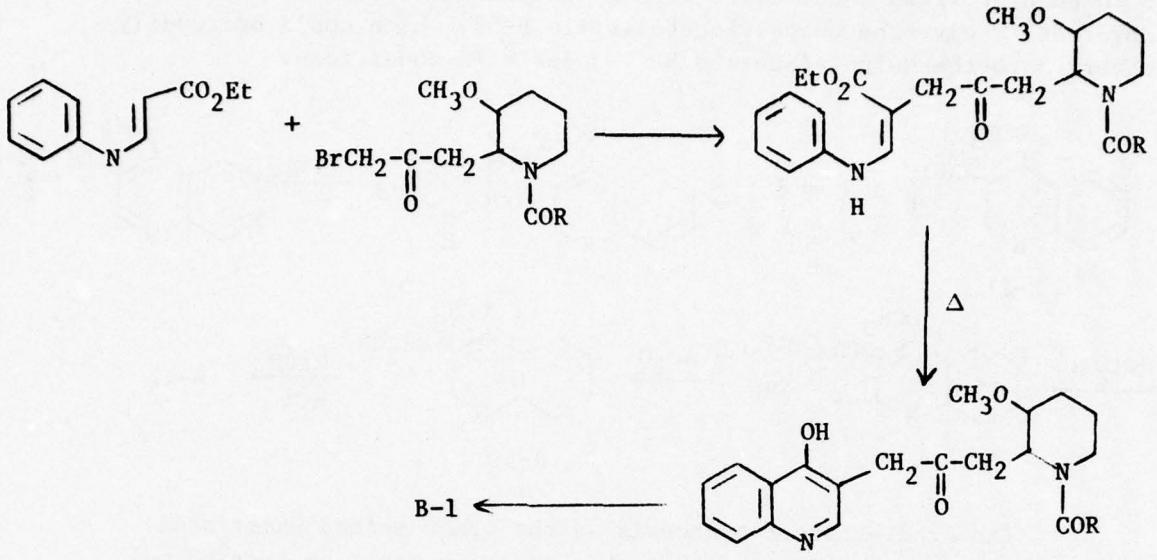
Two other methods have also been investigated. One of these starts from 4-methoxy-3-quinolylcarboxaldehyde (B-21). According to the method of Julian and Sturgis,[22] the rhodanine derivative of this aldehyde is to be hydrolyzed and treated with hydroxylamine followed by acetic anhydride to give the quinolylacetonitrile B-58, which could be readily converted to the quinolylacetate B-47 under mild conditions.



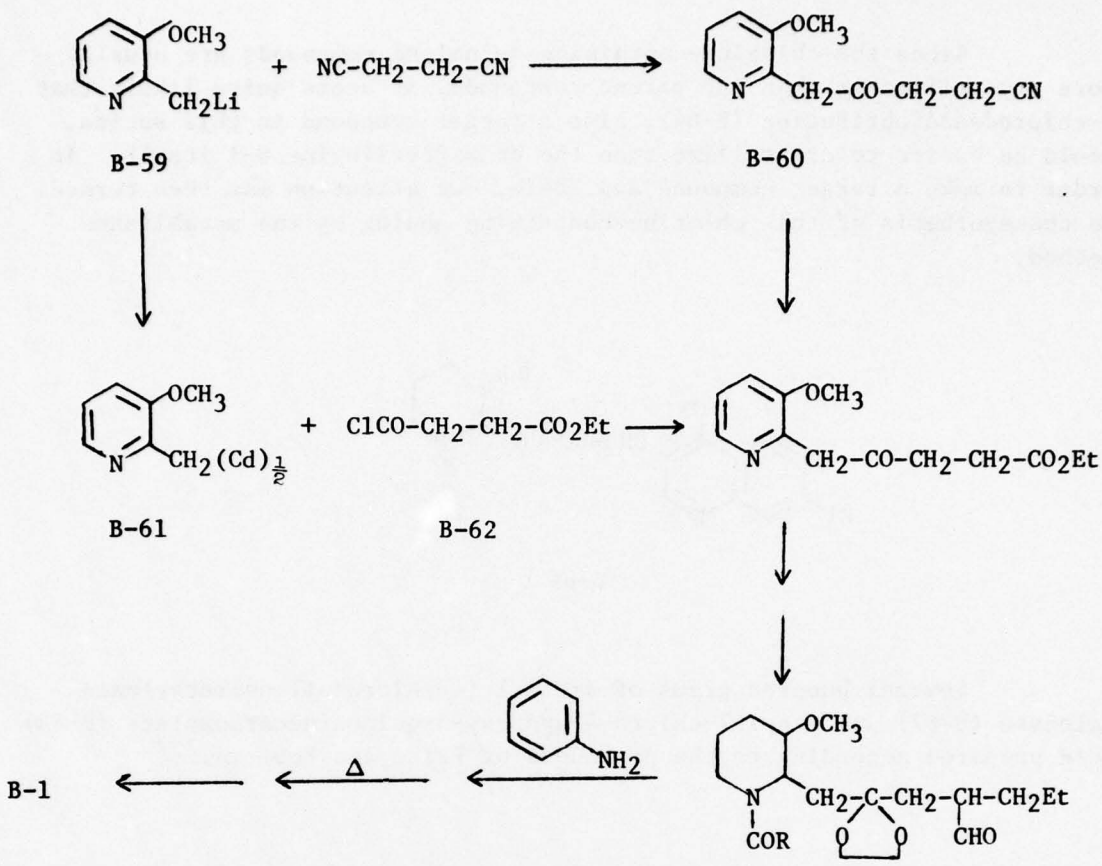
The Arndt-Eistert synthesis is the other method under study. Recent literature[23] indicated that this reaction could be carried out under mild conditions. In one experiment, only a trace of B-47 was obtained, the structure of which was proved by NMR. The reaction will be studied again.



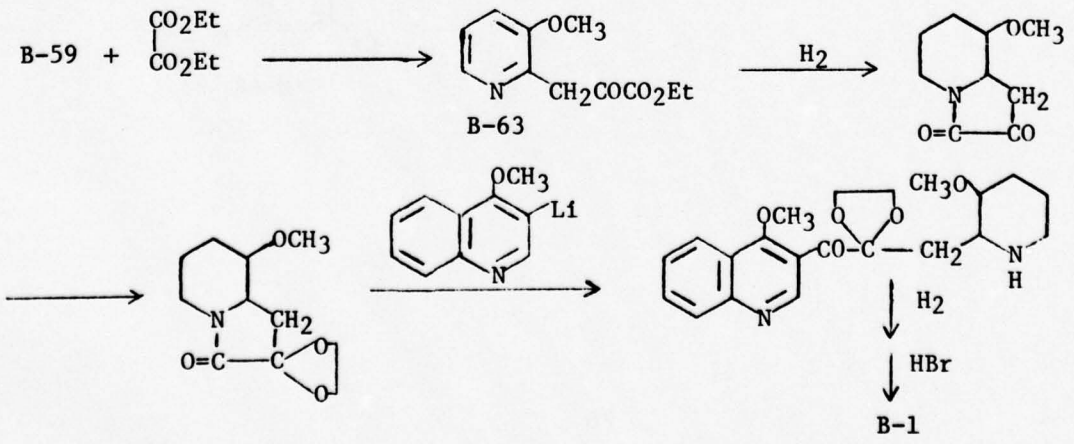
3. Construction of the Entire Side Chain portion prior to the cyclization of the Quinoline Ring.



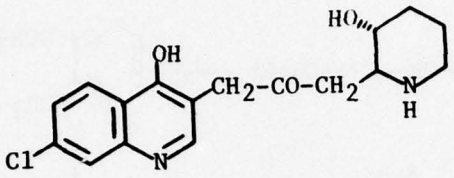
The general approach and background were presented in the last progress report. During this report period, an experiment was carried out to determine if the ketonitrile intermediate B-60 could be obtained by the reaction of the picolyllithium B-59 with a large excess of succinonitrile. This reaction was of no practical use since it yielded a quite complex mixture of the products. We are presently studying the reaction of the picolylcadmium compound B-61 with the acyl chloride B-62. If the desired product could be obtained successfully, further transformation reactions, including the final ring closure, should lead to the target compound B-1.



A different route to the target compound B-1, shown in the following scheme, was briefly examined. The α-keto ester B-63 was obtained in low yield (8%) by the reaction of α-picolyllithium with diethyl oxalate. In order to improve the yield of the α-keto ester intermediate, a model reaction using α-picoline as the starting material was conducted according to the method of Amstutz and Besso,[24] but we were unable to reproduce even the 10% yield of the desired product reported by them. Because of the difficulty anticipated in the preparation of enough starting material, the approach is not being continued.

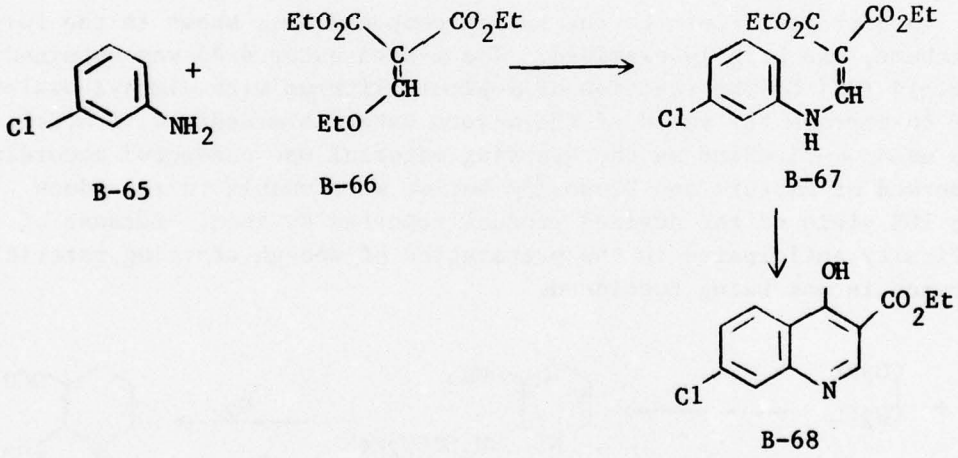


Since the chlorine-containing quinoline compounds are usually more crystallizable than the parent compounds, it seems quite likely that 7-chlorodeazafebrifugine (B-64), also a target compound in this series, would be easier to crystallize than the deazafebrifugine B-1 itself. In order to make a target compound available, our attention was then turned to the synthesis of this chlorine-containing analog by the established method.



B-64

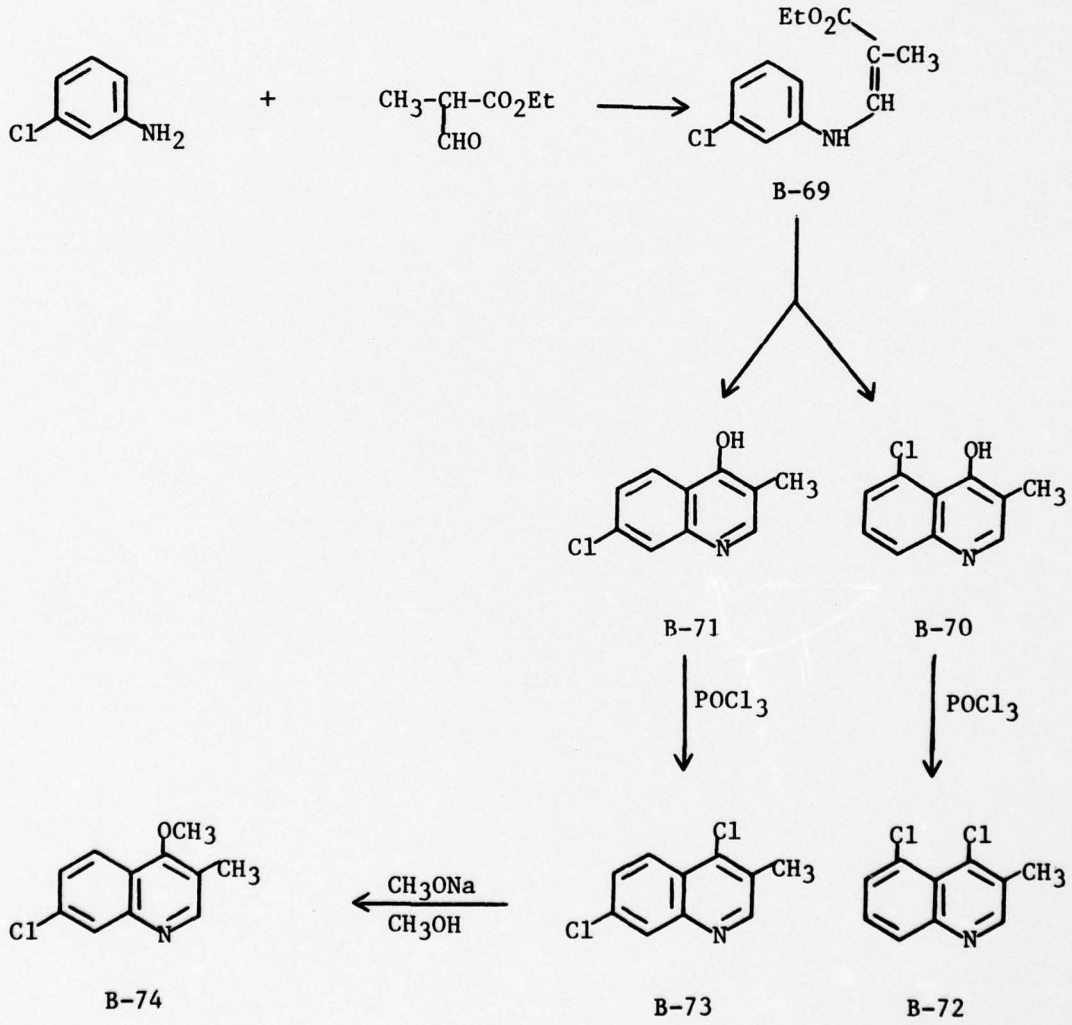
Several hundred grams of diethyl (m-chloroaniline)methylene-malonate (B-67) and ethyl 7-chloro-4-hydroxy-3-quinolinecarboxylate (B-68) were prepared according to the procedure of Price and Roberts.[25]



B-65 B-66 B-67

B-68

Another intermediate B-74 required in this synthesis was prepared by essentially the same method used for the preparation of 4-methoxy-3-methylquinoline. Compound B-69 obtained from m-chloroaniline and ethyl formylpropionate was cyclized in boiling Dowtherm A to yield a mixture of 5- and 7-chloro-4-hydroxy-3-methylquinoline (B-70 and B-71) in the ratio of 1:2. These isomers were separated by acetone extraction in a Soxhlet apparatus. The 5-chloro compound, being more soluble in acetone, was obtained first, while the 7-isomer was left behind in the thimble. On reaction with phosphorous oxychloride, these two compounds were converted to their respective chloro compounds B-72 and B-73. The structure of these compounds was established by comparison of their melting points with those reported in the literature,[26] and also by NMR. 7-Chloro-4-methoxy-3-methylquinoline (B-74) was prepared from 4,7-dichloro-3-methylquinoline (B-73) by the usual treatment with sodium methoxide in methanol.



Attempts were then made to lithiate 7-chloro-4-methoxy-3-methylquinoline (B-74) with lithium diisopropylamide in the usual manner. However, in contrast to 4-methoxy-3-methylquinoline, the chlorine-containing methylquinoline B-74 could not be so readily lithiated. At -65°, the chlorine atom appeared to be attacked, probably by the benzylic lithium formed in the reaction, which must be more reactive than butyllithium. On the other hand, when the reaction temperature was kept at below -72°, the methyl group was not lithiated even in the presence of large excess of lithium diisopropylamide, as indicated by the absence of deuterium incorporation after deuterium oxide quenching. Interestingly, deuterium exchange with 8-H of the quinoline ring was detected by NMR. A few more pilot scale experiments will be conducted to determine if the desired lithiation reaction could be successfully carried out.

III. EXPERIMENTAL

1-Cyclopropylbutan-1-one (A-4)

To a stirred suspension of 9 g of Mg and 250 ml of anhydrous Et_2O was added, under N_2, 5 g of propyl bromide (Aldrich) to initiate the reaction. As the reaction commenced, the remaining 40 g of propyl bromide was added dropwise to the suspension at such a rate that the Et_2O refluxed gently. The dark solution thus obtained was stirred for an additional hour followed by dropwise addition of 25 g of cyclopropyl cyanide (A-3, Aldrich). The reaction mixture was gently refluxed throughout the addition, then was allowed to stir at room temperature overnight. The resulting clear solution was poured into a mixture of 500 ml of 1 M H_2SO_4 and 200 g of crushed ice. The ether layer was separated and the aqueous layer extracted with Et_2O (2 x 150 ml). The combined Et_2O solution was dried ($MgSO_4$) and evaporated to give 33.5 g (81% yield) of A-4[3] as a liquid. Its ir spectrum (neat) showed a carbonyl absorption at 1700 cm^{-1}. No nitrile absorption was observed.

1-Bromo-4-heptanone (A-5)

A mixture of 29.5 g (0.267 mole) of A-4 and 250 ml of 48% HBr was stirred at room temperature for 20 hr. The resulting organic layer was separated and diluted with 200 ml of Et_2O. The ether solution was washed with 5% $NaHCO_3$ (2 x 100 ml), dried ($MgSO_4$) and evaporated to yield a liquid. Distillation of the liquid at 86°/3.5 mm gave 34.4 g (66% yield) of A-5 (lit.[27] bp 66°/1.5 mm).

Compound A-5 showed a strong carbonyl absorption at 1710 cm^{-1} in its ir spectrum (neat); its nmr spectrum ($CDCl_3$) showed a triplet at δ 0.9 (J = 3 cps; 3H; CH_3), a multiplet at δ 1.3-2.8 (8H; CH_2 at C-2, -3, -5, -6), a triplet at δ 3.45 (J = 6 cps; 2H; CH_2 at C-1); its mass spectrum had parent peaks at m/e:192 and 194 (Br isotope) of equal intensity.

1-Bromo-4-hydroxyheptane (A-6)

To a solution of 20.4 g (0.105 mole) of A-5 in 105 ml of THF at 2° was added dropwise, with stirring, 105 ml of 1 M BH_3-THF (Aldrich) in 1.5 hr. The temperature of the reaction mixture was kept below 10° during the addition as well as 1.5 hr after the addition. The cooling bath was then removed and the reaction mixture was allowed to warm up to room temperature in 1 hr. The mixture was cooled again to 2° and to it was added dropwise 30 ml of EtOH to decompose the excess diborane. The resulting solution was acidified with 2 ml of 60% ethanolic HCl and evaporated

in vacuo below 40°. The liquid residue was dissolved in 200 ml of Et_2O and the solution washed successively with 5% $NaHCO_3$ (30 ml), H_2O, and saturated with a NaCl solution. After being dried with $MgSO_4$, the ether solution was evaporated to yield crude A-6. This was divided into two portions and subjected to molecular distillation at 80° (0.3 mm) to give a combined yield of 12.1 g (58%) of A-6. Its ir spectrum (neat) had a strong absorption at 3560-3050 cm^{-1}. No carbonyl absorption for the starting ketone was observed. This compound was rather unstable on standing. It was therefore used immediately for the preparation of A-7.

1,4-Dibromoheptane (A-7)

To a solution of 6.7 g (0.034 mole) of A-6 and 11 g (0.042 mole) of triphenylphosphine in 80 ml of dry DMF cooled in an ice water bath was added dropwise, with stirring, 2.4 ml of Br_2 until a faint orange color persisted. The reaction solution was allowed to warm slowly to room temperature in 1.5 hr, then stirred at room temperature over night. The HBr formed in the reaction was removed by means of an aspirator (ca. 30 min). The solution was then heated at 60° for 30 min and distilled in vacuo. The initial fraction (100 ml) collected at 30-60°/1.5-3.0 mm was mostly DMF with a small amount of product; the second fraction (5 ml) collected at 50-75°/0.3 mm was mostly the desired product contaminated with DMF and a white solid. These two fractions were combined and diluted with 500 ml of H_2O. The aqueous solution was extracted with Skelly B (3 x 100 ml). The extract was dried ($MgSO_4$) and evaporated to yield A-7 as a liquid.

The preceding procedure was repeated using 5.4 g (0.028 mole) of A-6, 7.6 g (0.029 mole) of $Ø_3P$, 40 ml of DMF and 4.65 g of Br_2. The crude products from these two experiments were combined (12 g) and distilled to give 10.2 g (64% yield) of pure A-7, bp 63-65°/0.4 mm (lit.[28] bp 80-82°/4 mm). Its ir and nmr confirmed the structural assignment.

N-(4-Bromoheptyl)phthalimide (A-8)

A mixture of 10.1 g (0.039 mole) of A-7, 14.4 g (01078 mole) of potassium phthalimide, and 150 ml of Me_2CO was refluxed for 3 days. The solid was separated by filtration, washed with Me_2CO, and discarded. The combined acetone solution was evaporated to yield a liquid residue. This was column chromatographed on silica gel (Woelm Act I, 120 g) and eluted with $CHCl_3$. The first 380-ml fraction was discarded. The second 1,200-ml fraction contained 10.1 g (82% yield) of analytically pure A-8, which solidified on standing, mp 46-50°. The third 1,000-ml fraction contained 2 g of an oily liquid, which was partially solidified on standing. This fraction contained two other compounds in addition to A-8, as detected by tlc.

Compound A-8 had a carbonyl absorption at 1710 cm^{-1} (strong) and 1770 cm^{-1} (medium) in its ir spectrum (neat). Its nmr spectrum ($CDCl_3$) showed a triplet at δ 0.88 (J = 7 cps, 3H, CH_3), a multiplet at δ 1.20-2.00 (8H, CH_2 at C-2, -3, -5, -6), a multiplet at δ 3.50-3.75 (2H, CH_2 at C-1), a multiplet at δ 3.86-4.15 (1H, CH) and a multiplet at δ 7.50-7.82 (4H, aromatic H_S).

Anal. Calcd. for $C_{15}H_{18}BrNO_2$: C, 55.55; H, 5.60; N, 4.32. Found: C, 55.47; H, 5.96; N, 4.30.

6-Methoxy-4-methyl-8-(1-phthalimido-4-heptylamino)quinoline (A-9)

A mixture of 3.24 g (0.01 mole) of A-8, 1.5 g (0.008 mole) of 8-amino-6-methoxy-4-methylquinoline, 1.0 g (0.01 mole) of diisopropylamine, 2 ml of ethanol, and 2 ml of 2-ethoxyethanol was gradually heated in a steel container to 160° in 6 hr and maintained at that temperature for an additional 18 hr. The container was cooled to room temperature and the dark brown reaction mixture was transferred to a flask containing 120 ml of Et_2O. The mixture was stirred for 1 hr and filtered. The remaining solid was suspended in another 120-ml portion of Et_2O, stirred for 1 hr and filtered. The solid was discarded and the combined filtrate was evaporated. The residual liquid was dissolved in 5 ml of $CHCl_3$ and column chromatographed on 50 g of silica gel (Woelm, Act I) eluting with $CHCl_3$. The first 550-ml fraction contained 1.2 g of starting material A-8. The second 185-ml fraction contained 1.1 g (30% yield) of the desired product A-9. The third 145-ml fraction contained both A-9 and the starting aminoquinoline.

Compound A-9 had a weak NH absorption at 3350 cm^{-1} and carbonyl absorptions at 1770 cm^{-1} (medium) and 1710 cm^{-1} (strong) in its ir spectrum (neat). Its nmr spectrum was also in accord with the assigned structure.

8-(1-Amino-4-heptylamino)-6-methoxy-4-methylquinoline (A-10)

A stirred solution of 1.1 g (2.5 mmole) of A-9, 0.8 ml of 85% hydrazine and 25 ml of EtOH was refluxed for 2 hr. The white precipitate was filtered, washed with 5 ml of EtOH, and discarded. The combined ethanol solution was evaporated and the residue was dissolved in 10 ml of 30% KOH. The resulting aqueous solution was extracted with Et_2O (3 x 25 ml). The ether solution was dried ($MgSO_4$) and evaporated. The residual liquid was subjected to a bulb-to-bulb distillation. The initial fraction collected at an oven temperature of 110° (0.15 mm) was discarded. The second fraction collected at an oven temperature of 140° (0.15 mm) was the desired compound A-10, 0.3 g (40% yield), isolated as a light yellow liquid. Its ir spectrum (neat) had NH and NH_2 absorptions at 3350 and 3280 cm^{-1} (medium). Its nmr spectrum showed a triplet at δ 0.86 (J = 7 cps, 3H, CH_3 on the alkyl chain),

a multiplet at δ 1.20-1.80 (8H, CH_2 protons excluding the ones α to NH_2), a singlet at δ 2.46 (3H, CH_3 at position 4 of the quinoline ring), a multiplet at δ 2.20-2.70 (2H, CH_2 protons α to NH_2), a multiplet at δ 2.60-2.26 (1H, CH), a singlet at δ 3.78 (3H, CH_3O), a multiplet at δ 5.94-6.32 (2H, aro-H), a doublet at δ 7.01 (J = 4 cps, 1H, aro-H) and a doublet at δ 8.32 (J = 4 cps, 1H, aro-H). Mass spec: m/3 301 (M^+), 189 (100%, the 8-amino-6-methoxy-4-methylquinoline moiety), 243 (84.5%, M+ - $(CH_2)_3$-NH_2), 257 (1.83%, M+ - $CH_2CH_2NH_2$), 229 (0.7%, M+ - $(CH_2)_4$-NH_2). The fragmentation pattern was very similar to that of previously synthesized 8-(1-ethyl-4-aminobutylamino)-6-methoxy-4-methylquinoline.

6-Methoxy-4-methyl-8-(1-propyl-4-aminobutylamino)quinoline diphosphate (A-2b)

To a solution of 0.3 g of A-10 in 0.5 ml of 2-propanol was added a solution of 0.3 g of 85% H_3PO_4 in 0.5 ml of 2-propanol. The precipitated brown paste was separated and dissolved in ca. 5 ml of boiling, 95% EtOH. On cooling, a yellow-brown oil separated. The ethanol solution was decanted and the oil redissolved in hot, 95% EtOH. Again a yellow-brown oil separated on cooling but this time it solidified on over night standing to give 0.1 g of A-2b. Three additional recrystallizations from 95% EtOH yielded an analytically pure sample, mp 142-144°.

Anal. Calcd. for $C_{18}H_{27}N_3O \cdot 2H_3PO_4 \cdot 2H_2O$: C, 40.50; H, 6.99; N, 7.87; P, 11.62. Found: C, 40.41; H, 6.78; N, 7.86; P, 11.74.

4-[(5-Diethylamino-2-pentyl)amino]-5-nitroveratrole (A-11)

The experiment on p. 16 of MRI-2883-B Quarterly Report No. 45 was repeated. The crude, black syrup (which decomposed on attempted distillation) was dissolved in 15 ml of CH_2Cl_2 and chromatographed through a neutral alumina (Fisher) column. Elution with petroleum ether (bp 60-90°) and 5% CH_2Cl_2-petroleum ether gave a small amount of starting material. Continued elution with CH_2Cl_2 followed by EtOAc gave the product A-11.

An alternative procedure to isolate A-11 was also conducted. After elution of the column with petroleum ether, the adsorbent was removed from the column and the section, which contained the desired product, was extracted with $CHCl_3$. The compound was used in the following reaction without further purification.

1-(5-Diethylamino-2-pentyl)-5,6-dimethoxybenzimidazole (A-13)

A mixture of 6.4 g (0.02 mole) of A-11, 75 ml of EtOH, and 0.2 g of PtO_2 was hydrogenated for 16 hr on a Parr hydrogenator at 65 psig. The catalyst was removed by filtration and the solvent evaporated under reduced pressure. To the residual liquid was added 50 ml of 98% HCO_2H and the mixture was heated in a stainless steel vessel for 3 hr at 165°. The mixture was cooled and the dark liquid evaporated under reduced pressure to remove the excess HCO_2H. The residue was dissolved in 25 ml of H_2O, made strongly basic with 20% NaOH, and extracted with Et_2O (5 x 30 ml). Evaporation of the ether extract gave 2 g of a dark oil. Its uv spectrum showed a characteristic benzimidazole absorption at 292 nm (pH 1). Repeated attempts to prepare a crystalline salt failed. The oily product, after evaporation of solvents, was subjected to short path distillation in a Kugelrohr (ball tube oven). There was obtained 1.5 g (23% yield) of A-13 as an orange liquid, bp 150-155°/0.05 mm; ir: 1655, 1500 cm^{-1}; uv: $\lambda_{Max}^{pH\ 1}$ 292 nm (t 16,200); mass spec: 319 (M^+).

Anal. Calcd. for $C_{18}H_{29}N_3O_2 \cdot 1.5\ H_2O$: C, 62.40; H, 9.31; N, 12.13. Found: C, 62.61; H, 9.87; N, 11.76.

Attempted preparation of A-13 by refluxing the HCl salt of A-12 with 98% HCO_2H for 3 hr, by refluxing the salt with a mixture of HCO_2H and $HCONH_2$ or by refluxing the free base A-12 with HCO_2H did not yield the desired product. A very small amount of A-13 was obtained when A-12 was heated with a mixture of Ac_2O and $HC(OEt)_3$.

4-(5-Dimethylamino-2-pentylamino)-3-nitroanisole (A-15)

A mixture of 3.5 g (0.015 mole) of 4-bromo-3-nitroanisole (A-14), 2.5 g (0.015 mole) of 5-diethylamino-2-pentylamine (novoldiamine), and 1.3 g (0.015 mole) of sodium bicarbonate was heated, with stirring, at 120° for 5 hr under nitrogen. There was much gas evolution. The dark reaction mixture was cooled and extracted with ether (5 x 20 ml). The ether extract was dried and evaporated. TLC (CH_2Cl_2 on alumina) of the syrupy residue showed two spots. Chromatography of the residue on silica gel (MCB) with petroleum ether gave a 66% recovery of the starting material A-14. Further elution with CH_2Cl_2 gave 1 g (22% yield) of the product A-15 as a red liquid. R_f : 0.2 (CH_2Cl_2 on alumina), b.p. 160-165°/0.03 mm; ir : 2.95, 6.3, 6.6 ; m/e : 309 (M^+).

In the absence of sodium bicarbonate, only up to 13% yield of A-15 was obtained even when the reaction mixture was heated to 180°. A 16% yield of A-15 was realized when copper powder was used as the catalyst. When pyridine was used as a reaction solvent, a 22% yield of A-15 was obtained at reflux temperature of pyridine. Higher temperature (160°) resulted in extensive decomposition.

1-(5-Dimethylamino-2-pentyl)-5-methoxybenzimidazole (A-17)

A mixture of 6.2 g (0.02 mole) of A-15, 75 ml of ethanol, and 0.2 g of PtO_2 was hydrogenated at 60 psig for 5 hr. The catalyst was removed by filtration and the solvent evaporated under reduced pressure. To the residue was added 50 ml of 98% formic acid and the mixture heated in a stainless steel pressure vessel at 165° for 3 hr. The reaction mixture was cooled and excess formic acid removed. This was diluted with 25 ml of water and made basic with 20% sodium hydroxide. The resulting mixture was extracted with ether (5 x 30 ml). The ethereal extract was dried, evaporated, and the residual oil distilled in a Kugelrohr to give 4.3 g (74% yield) of A-17 as a pale yellow viscous liquid, b.p. 122-127°/0.05 mm (lit.[29] b.p. 195°/2 mm); ir : 3.1, 5.9, 6.3 μ; λ_{max}^{EtOH} 250 (ϵ 15,200), 292 nm (ϵ 10,900); $\lambda_{max}^{pH\ 1}$ 285 nm (ϵ 12,600); m/e : 289 (M^+)

Anal. Calcd. for $C_{17}H_{27}N_3O \cdot 1.5H_2O$: C, 64.52; H, 9.56; N, 13.28. Found: C, 64.45; H, 9.55; N, 13.22.

Ethyl 3-Methoxy-2-pyridylacetate (B-7)

A solution of lithium diisopropylamide was prepared from 0.12 mole of distilled diisopropylamine and 0.12 mole of a hexane solution of BuLi (50 ml x 2.4 M) in 70 ml of Et_2O at ice bath temperature under N_2. After 30 min of stirring, 12.3 g (0.1 mole) of 3-methoxy-2-methylpyridine (B-5) in 30 ml of Et_2O was added dropwise over a period of 15 min. Stirring was continued in the cold for 1 hr. The mixture was then poured over 100 g of finely powdered Dry Ice and the solvent was allowed to evaporate. The residue was taken up in 400 ml of absolute EtOH and the solution saturated with anhydrous HCl for 1 hr with cooling. After being allowed to stand at room temperature overnight, EtOH was evaporated under reduced pressure at 30°. The residue was triturated with 200 ml of $CHCl_3$ and neutralized with a saturated K_2CO_3 solution. The mixture was stirred for 30 min, the solids removed by filtration and the chloroform solution separated. The chloroform solution was washed (H_2O), dried (Na_2SO_4) and evaporated. The resulting residual liquid was initially distilled under water-aspirator pressure to remove the unreacted starting material and then in vacuo to give 9.1 g (47% yield) of the desired product B-7 as a yellow oil, b.p. 95-98° (0.5 mm). It was identical with the material prepared by a different method as described in our previous annual progress report.[1]

Ethyl 1-Acetyl-3-methoxy-2-piperidylacetate (B-3)

The pyridylacetate B-7, 9.1 g, was dissolved in 150 ml of EtOH and hydrogenated at 50 psig in the presence of 3 g of 5% rhodium-on-charcoal catalyst at room temperature for 1 day. After removal of the catalyst, the solution was evaporated under reduced pressure at 40° to give a clear liquid. NMR showed that the reduction was essentially complete. The crude hydrogenation product B-8 was treated with 20 ml of Ac_2O for 30 min. Water was then added to hydrolyze excess Ac_2O. The mixture was evaporated and the residual oil was distilled to afford 7.2 g of the desired product B-3 as a yellow oil, b.p. 135-138° (1.5 mm).

Ethyl 2-Formylpropionate

To a mixture of 46 g (2 g-atoms) of sodium and 222 g (3 moles) of ethyl formate in 500 ml of anhydrous ether was added a small portion of 204 g (2 moles) of ethyl propionate. After the reaction was started, the remaining ethyl propionate was added over a period of 1.5 hr. The mixture was stirred for two more hours and then allowed to stand at room temperature overnight. Water (500 ml) was added to dissolve the solid formed, and the ether layer was separated and discarded. The aqueous solution was acidified with hydrochloric acid and the red oily product separated. The aqueous layer was extracted with ether and the ether extract combined with the oil. It was washed (H_2O), dried (Na_2SO_4) and distilled to give 45 g (35% yield) of the product as a yellow oil, b.p. 40-85° (20 mm).

4-Hydroxy-3-methylquinoline (B-9)

To 45 g (0.35 mole) of ethyl α-formylpropionate was added 35 g (0.35 mole) of aniline. The exothermic reaction started immediately. After the reaction subsided, a solid product slowly separated. It was filtered and washed with cyclohexane. The yield of the anil was 30 g, yellow crystals, m.p. 76-77°.

The crude anil was dropped into Dowtherm A at 220° and the mixture was heated with stirring at 240-250° for 30 min. On cooling, solid product separated out. It was collected by filtration and washed with Skelly F. There was obtained 15 g of the desired product B-9, m.p. 228-230° (lit.[10] 231°) (yield 27%).

3-Methyl-4-methoxyquinoline (B-10)

Fifteen grams of 4-hydroxy-3-methylquinoline (B-9) was heated with 80 ml of phosphorous oxychloride on a steam bath for 2 hr. The mixture was distilled under reduced pressure to remove excess phosphorous oxychloride. The residue was poured onto ice chips and made basic with ammonium hydroxide. The solid formed was filtered to give 17 g of 4-chloro-3-methylquinoline, m.p. 55° (lit.[10] m.p. 60°).

The crude 4-chloro-3-methylquinoline was heated under reflux with a freshly prepared sodium methoxide solution (prepared from 6 g of sodium and 50 ml of methanol) for 1 day. The mixture was diluted with water (400 ml) and the resulting oil was extracted with ether (2 x 200 ml). The combined ether extract was washed (H_2O), dried ($MgSO_4$) and evaporated to furnish 14 g of 3-methyl-4-methoxyquinoline (B-10) as an oily liquid.

Attempted Metalation of 3-Methyl-4-methoxyquinoline and Reaction with Ethyl 1-Acetoxy-3-methoxy-2-piperidylacetate

This experiment was carried out according to the method of Raynolds and Levine.[8] To a mixture of 10 g of 40% sodium dispersion in mineral oil and 70 ml of benzene was added with stirring a few milliliters of a bromobenzene solution in benzene (1:1), followed by 1 ml of 10% amyl alcohol in benzene. The temperature of the reaction mixture was maintained at 30 ± 3°. More amyl alcohol solution was added as needed to initiate the reaction. The color of the mixture darkened as the reaction proceeded. The remainder of the bromobenzene solution was added in 20 min. The mixture was stirred for 2 hr, while the temperature was maintained at below 30°. It was then cooled in an ice bath and a solution of 8.5 g of diisopropylamine in 10 ml of benzene was added. After the mixture was stirred for 30 min, a solution of 13 g of crude 3-methyl-4-methoxyquinoline in 20 ml of benzene was added. No appreciable increase in the temperature was noticed. It was stirred for 30 min and a benzene solution (1:1) of 9 g (0.037 mole) of ethyl 1-acetoxy-3-methoxy-2-piperidylacetate was introduced. Stirring was continued for one more hour. The reaction mixture was poured into water (200 ml) and the benzene layer was separated. The aqueous solution was extracted with ether. The combined organic layer was washed (H_2O), dried (Na_2SO_4) and evaporated. The residue was found to be the unreacted 3-methyl-4-methoxyquinoline. A small amount of the piperidylacetate was also recovered by chloroform extraction of the aqueous phase.

4-Chloro-3-quinolinemethanol (B-13)

A suspension of 9.0 g (0.12 mole) of 52% oil protected lithium aluminum hydride in 300 ml of ether was cooled to -60°. To this suspension was added a solution of 23.6 g (0.1 mole) of 4-chloro-3-carbethoxy-quinoline (B-12) in 300 ml of the same solvent at such a rate that the reaction temperature was maintained at below -50°. After the addition was completed, the mixture was stirred at -50° for 2 hr. The cooling bath was then removed and when the temperature reached -25°, 150 ml of water-saturated ether was added. It was followed by a solution of 15 g of sodium hydroxide in 40 ml of water. Stirring was continued for 1 hr. The ether layer was separated and the solid was filtered with Celite. The filter cake was extracted continuously with acetone to afford 8.7 g (45% yield) of 4-chloro-3-quinolinemethanol (B-13), m.p. 147-148°. It was recrystallized from acetone as beige needles, m.p. 148-149° (lit.[12] 147-147.5°). From the ether layer a little unreacted starting material was recovered.

4-Hydroxyquinoline (B-17)

This compound was prepared by the method of Riegel, et al.[30] Ethyl 4-hydroxy-3-quinolinecarboxylate, 35 g, was boiled with 200 ml of 10%. NaOH solution for 2 hr. The mixture was cooled, diluted with H_2O (500 ml) and made acidic with hydrochloric acid. The white precipitate was isolated by filtration and washed with water. The crude 4-hydroxy-3-quinolinecarboxylic acid (B-16) thus obtained was placed in a flask and heated rapidly with open flame. Effervescence occurred when the solid started to melt. Heating was continued until gas evoluation ceased. The residue solidified rapidly and was recrystallized from EtOH to give 18 g (77% yield) of the desired product as white crystals, mp 196-199°.

3-Bromo-4-hydroxyquinoline (B-18)

Surrey and Cutler's method[31] was used for this preparation. Bromine, 21.6 g (0.12 mole), was added in small portions, with shaking, to a solution of 18 g (0.12 mole) of B-2 in 150 ml of AcOH. The mixture was heated on a steam bath for 30 min. After cooling, the solid product was isolated by filtration, washed with AcOH and dissolved in 300 ml of 10% NaOH. The NaOH solution was then saturated with CO_2 and the precipitate was collected by filtration to give 26 g of crude product, mp 280-283° (93% yield). It was recrystallized from EtOH to yield white crystals, mp 287-290° (lit.[31] mp 281-282°).

Anal. Calcd. for C_9H_6BrNO: C, 48.24; H, 2.70; N, 6.25. Found: C, 48.39; H, 2.70; N, 6.01.

3-Bromo-4-chloroquinoline (B-19)

Twenty-six grams of B-18 was added slowly to 150 ml of $POCl_3$. The mixture was heated under reflux for 3 hr. Excess $POCl_3$ was removed by distillation, the residue was poured over 800 g of crushed ice and made basic with NaOH solution. The precipitated product was collected by filtration and washed with water. There was obtained 26.6 g (95% yield) of B-19, m.p. 64-65° which, on recrystallization from MeOH, gave white needles, m.p. 68-70° (lit.[31] m.p. 67-68°).

Anal. Calcd. for C_9H_5BrClN: C, 44.57; H, 2.08; N, 5.78. Found: C, 44.92; H, 1.71; N, 5.53.

3-Bromo-4-methoxyquinoline (B-20)

To a freshly prepared NaOMe solution in 100 ml of MeOH (from 3 g of Na) was added 12 g of B-19. The mixture was heated under reflux, with stirring, for 2 hr. It was then poured into 500 ml of H_2O and the solvent was evaporated under a stream of air. The solid product, m.p. 87-88°, was collected by filtration, to give 9.5 g (80% yield) of B-20. It was recrystallized from MeOH as white needles, m.p. 89-91°.

Anal. Calcd. for $C_{10}H_8BrNO$: C, 50.45; H, 3.39; N, 5.88. Found: C, 50.77; H, 3.55; N, 5.67.

4-Methoxy-3-quinolinecarboxaldehyde (B-21)

To a cooled solution of 1.65 g (7 moles) of B-20 in 70 ml of Et_2O was added, under N_2, one equivalent of a 2.4 M BuLi solution in hexane, at -70°. The mixture was stirred at that temperature for 1 hr followed by addition of 1 ml of DMF in 10 ml of Et_2O (5 min). Stirring was continued for 1.5 hr while the temperature of the reaction mixture was allowed to reach -10°. Water was added and the ether layer separated. It was washed (H_2O), dried (Na_2SO_4) and evaporated to give 0.9 g of a yellow solid, m.p. 109-110° (68% yield). It was recrystallized from chloroform-cyclohexane as pale yellow needles (somewhat sensitive to air), m.p. 110-112°. The product showed the expected carbonyl absorption at 5.95 μ in ir.

Reaction of 3-Lithio-4-methoxyquinoline with Dimethylformamide--Formation of 4-Dimethylamino-3-quinolinecarboxaldehyde (B-25)

To a solution of 11.9 g (0.05 mole) of 3-bromo-4-methoxyquinoline (B-20) in 150 ml of ether cooled to -70°, was added 0.05 mole of butyllithium in hexane over a period of 30 min. The reaction temperature was maintained at below -65° during the addition of butyllithium. After the reaction mixture had been stirred for one more hour at -75°, 14 g of dimethylformamide was introduced. The temperature of the mixture was allowed to rise to -10° in 1.5 hr. Water (30 ml) was added and stirring was continued for 30 min. The ether layer was separated and washed with water. Yellow crystals soon started to separate from both the ether and water solutions. On filtration, there was obtained 5.1 g of yellow crystals, m.p. 127-129°. It was crystallized from methanol as yellow needle without further change of the melting point. This product was identified by NMR as 4-dimethylamino-3-quinolinecarboxaldehyde (B-25). A similar result was obtained when the reaction of the lithio derivative with dimethylformamide was quenched after 10 min.

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.97; H, 6.04; N, 13.99. Found: C, 72.05; H, 5.99, N, 14.22.

Diethyl (m-Chloroanilino)methylenemalonate (B-67).

To 255 g (2 molles) of m-chloroaniline (B-65) in an evaporating dish was added, in one portion, 455 g (2.1 moles) of diethyl ethoxymethylenemalonate (B-66). In contrast to the preparation of the unchlorinated analog, the temperature of the reaction mixture only rose to 56° after addition. The mixture was heated with stirring at 100-110° for 3 hr and cooled. The product, which solidified after standing overnight, was collected by filtration to give 555 g (94% yield) of B-67 as an off-white solid, mp 56-58°. Recrystallization from Skelly solve F (bp 35-60°) followed by recrystallization from EtOH yielded analytically pure B-67 as long, white needles, mp 59-60° (lit.[25] mp 55-56°).

Anal. Calcd. for $C_{14}H_{16}ClNO_4$: C, 56.48; H, 5.42; N, 4.70. Found: C, 56.29; H, 5.39; N, 4.64.

Ethyl 7-Chloro-4-hydroxy-3-quinolinecarboxylate (B-68)

To 150 ml of Dowtherm heated at 220° was added 120 g of B-67. The mixture was heated at 240-250° for 30 min whereupon the product gradually separated from the hot reaction mixture. The mixture was coded, diluted with 50 ml of EtOH, and filtered to give 103 g (quantitative yield)

of solid, mp > 300°. Recrystallization from DMF yielded analytically pure B-68 as a white powder, mp > 300° (lit.[25] mp 295-297°). The product was dried at 110° in vacuo for 6 hr before analysis.

Anal. Calcd. for $C_{12}H_{10}ClNO_3 \cdot \frac{1}{2}H_2O$: C, 55.29; H, 4.25; N, 5.37. Found: C, 55.20; H, 4.49; N, 5.18.

Ethyl 2-Anilinomethylenepropionate

The preparation of this compound from aniline and ethyl 2-formylpropionate was described in Annual Progress Report No. 10. The crude product was recrystallized from methanol as white crystals, m.p. 95-97°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.83. Found: C, 70.10; H, 7.53; N, 7.03.

Ethyl 2-(3-Chlorophenylaminomethylene)propionate (B-69)

This compound was prepared analogous to the above method from m-chloroaniline and ethyl 2-formylpropionate. The crude product was recrystallized from methanol as white crystals, m.p. 106-107°.

Anal. Calcd. for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.85. Found: C, 59.81; H, 6.15; N, 5.90.

5- and 7-Chloro-4-hydroxy-3-methylquinoline (B-70 and B-71)

Fifty-five grams of B-69 was added into 200 ml of Dowtherm A at 250-260° and the mixture was boiled for 15 min. On cooling, the product readily crystallized and was isolated by filtration. The crude product (22.5 g, 50% yield) thus obtained was extracted in a Soxhlet apparatus with acetone for 10 hr. The acetone extract was cooled and filtered to afford 7 g of a solid product which was later shown to be 5-chloro-4-hydroxy-3-methylquinoline (B-70). A small sample recrystallized from methanol as white crystals, m.p. 249-251° (lit.[26] m.p. > 250°).

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; N, 7.24. Found: C, 61.85; H, 4.08; N, 6.87.

The solid residue left in the thimble (13.8 g) was shown to be mainly mainly 7-chloro-4-hydroxy-3-methylquinoline (B-71) on its subsequent conversion to 4,7-dichloro-3-methylquinoline. It is only slightly soluble in methanol from which it was recrystallized as white crystals, m.p. > 320° (lit [26] m.p. > 300°).

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; N, 7.24. Found: C, 62.00; H, 4.48; N, 6.95.

4,7-Dichloro-3-methylquinoline (B-73)

7-Chloro-4-hydroxy-3-methylquinoline (B-71), 35 g, was heated with 120 ml of phosphorus oxychloride on a steam bath for 1 hr. Excess phosphorus oxychloride was removed by distillation under reduced pressure. The residue was poured onto crushed ice and made basic with sodium hydroxide. The precipitate was filtered, washed (H_2O) and dried. It was recrystallized from acetone to afford 24.5 g of 4,7-dichloro-3-methylquinoline as white needles, m.p. 82-83°. On further recrystallization a pure sample, m.p. 85-86° was obtained (lit.[26] m.p. 87.5-88°).

Anal. Calcd. for $C_{10}H_7Cl_2N$: C, 56.63; H, 3.33; N, 6.61. Found: C, 56.99; H, 3.62; N, 6.51.

4,5-Dichloro-3-methylquinoline (B-72)

This compound was prepared in a similar manner from 5-chloro-4-hydroxy-3-methylquinoline by the action of phosphorus oxychloride. However, the yield of the purified product was much lower. From 13 g of the hydroxyquinoline B-70 there was obtained only 4.5 g of the desired product as white needles, m.p. 71-72° (lit.[26] m.p. 72-72.5°).

Anal. Calcd. for $C_{10}H_7Cl_2N$: C, 56.63; H, 3.33; N, 6.61. Found: C, 56.52; H, 3.41; N, 6.58.

7-Chloro-4-methoxy-3-methylquinoline (B-74)

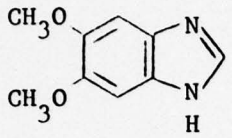
To a freshly prepared sodium methoxide solution in methanol (from 7.2 g of sodium and 150 ml of methanol) was added 21.2 g (0.1 mole) of 4,7-dichloro-3-methylquinoline (B-73). The reaction mixture was heated under reflux with stirring for 10 hr. Upon dilution with water (600 ml), an oily product separated, which slowly solidified. It was collected by filtration to give 17.5 g of 7-chloro-4-methoxy-3-methylquinoline (84% yield). On recrystallization from Skelly F, pure compound B-74 was isolated as white needles, m.p. 53-54°.

Anal. Calcd. for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.75; H, 5.11; N, 6.71.

IV. COMPOUNDS SUBMITTED FOR BIOLOGICAL STUDIES

MO-522 (BG-04029; WB-11-88B):

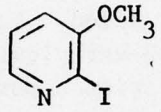
5,6-Dimethoxybenzimidazole



2.0 g

MO-523 (BG-04038; Y-II-92-2):

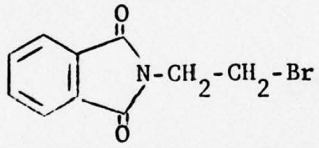
2-Iodo-3-methoxypyridine



3.0 g

MO-524 (BG-04047; Y-I-21-1):

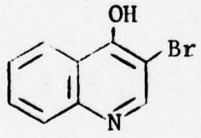
2-(Phthalimido)bromoethane



3.5 g

MO-525 (BG-09202; PC-VII-74):

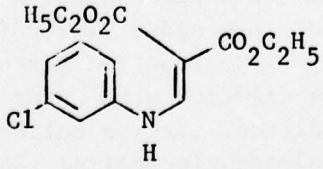
3-Bromo-4-hydroxyquinoline



2.0 g

MO-526 (BG-09211; CC-II-31):

Diethyl (m-chloroanilino)methylenemalonate



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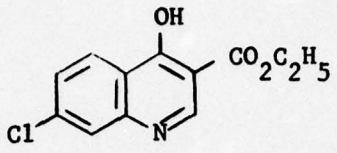
MO-527 (BG-10750; CC-II-33):

Ethyl 7-chloro-4-hydroxy-3-quinolinecarboxylate



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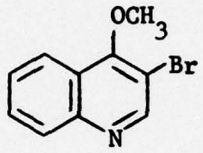
MO-528 (BG-10769; PC-VII-76):

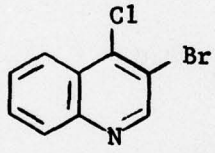
3-Bromo-4-methoxyquinoline



2.0 g

MO-529 (BG-11640; PC-VII-75):

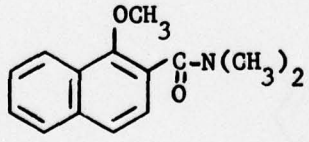
3-Bromo-4-chloroquinoline



2.0 g

MO-530 (BG-11659; PC-VII-63):

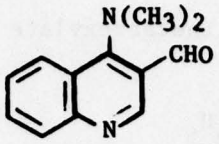
3-Dimethylaminocarbonyl-4-methoxyquinoline



2.0 g

MO-533 (BG-44201; PC-VIII-9):

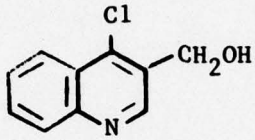
4-Dimethylamino-3-quinolinecarboxaldehyde



2 g

MO-534 (BG-44210; PC-VIII-12):

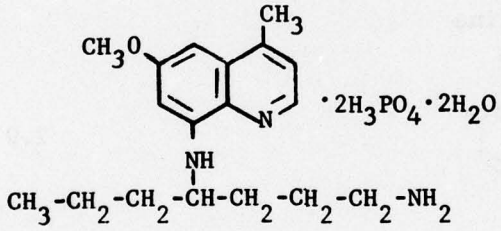
4-Chloro-3-quinolinemethanol



2 g

MO-535 (BG-46885; Y-3-84):

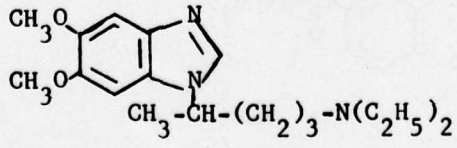
6-Methoxy-4-methyl-8-(1-propyl-4-aminobutylamino)-quinoline Diphosphate Dihydrate



2.2 g

MO-531(BG-21904; WB-12-18c):

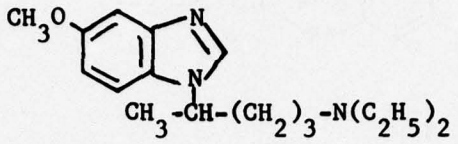
1-(5-Diethylamino-2-pentyl)-5,6-dimethoxybenzimidazole



4g

MO-532(BG-39059; WB-12-24):

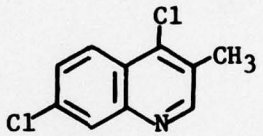
1-(5-Diethylamino-2-pentyl)-5-methoxybenzimidazole



2g

MO-536 (BG-60705; PC-VIII-35):

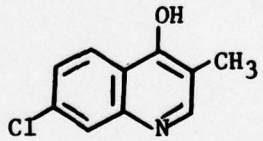
4,7-Dichloro-3-methylquinoline



2 g

MO-537 (BG-60714; PC-VIII-34):

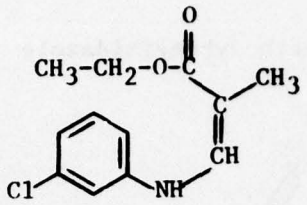
7-Chloro-4-hydroxy-3-methylquinoline



2 g

MO-538 (BG-60723; PC-VIII-33):

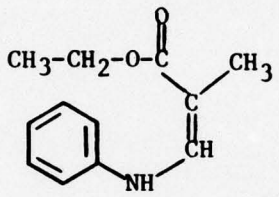
Ethyl 2-(3-Chlorophenylaminomethylene)propionate



2 g

MO-539 (BG-60732; PC-VIII-36):

Ethyl 2-(Anilinomethylene)propionate



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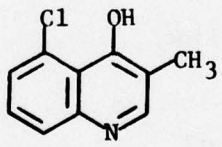
MO-540 (BG-63626; PC-VIII-38):

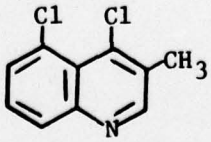
5-Chloro-4-hydroxy-3-methylquinoline



2 g

MO-541 (BG-63635; PC-VIII-39):

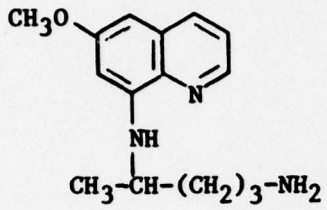
4,5-Dichloro-3-methylquinoline



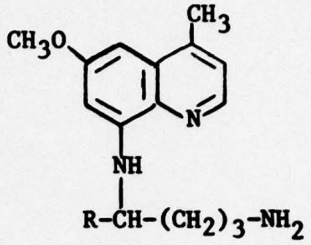
2 g

V. ANTIMALARIAL TEST RESULTS

Among 20 compounds submitted for antimalarial activity evaluation, 8-(6-amino-4-heptylamino)-6-methoxy-4-methylquinoline diphosphate [6-methoxy-4-methyl-8-(1-propyl-4-aminobutylamino)quinoline diphosphate, WR-226573, MO-535] displayed antimalarial activity against Plasmodium berghei.



Primaquine



R = C_2H_5 : WR-215761
R = $(CH_2)_2$-CH_3 : WR-226573

The activity of WR-226573 is comparable to that of primaquine but is much less toxic. A comparison of the activity of WR-226573 with that of primaquine[1,2] as well as that of the ethyl homolog (WR-215761), synthesized in our laboratory, is listed as follows.

	Dosage (mg/kg)							
	5	10	20	40	80	160	320	640
Primaquine[55]	--	--	+2.2	+4.2	+6.4	+7.0 (2 toxic)	5 toxic	5 toxic
Primaquine[56]	--	--	+4.0	+5.0	+9.4	+10.8 (2 toxic)	5 toxic	5 toxic
WR-215761	+2.1	+4.1	+7.3	+7.9	+9.7	+11.5	5 cures	5 cures
WR-226573	--	--	+3.1	+4.1	+5.7	+6.3	+9.1	+12.3

While the activity of WR-226573 is not as outstanding as that of WR-215761, it furnishes some very useful information for future structural modification work. The trifluoromethyl and the isopropyl analogs proposed in our research proposal B-1720, therefore, will be synthesized and studied.

WR-215761 was also found to exhibit outstanding prophylactic antimalarial activity in Dr. Schmidt's SR monkey tests.

	Dosage (mg/kg)				
	0.0625	0.125	0.25	0.5	1.0
WR-216571	0/2 cures	6/7 cures	4/4 cures	1/1 cures	1/1 cures

VI. REFERENCES

1. MRI Annual Progress Report No. 10 to U.S. Army Medical Research and Development Command. Contract DADA-49-193-MD-2749.

2. Cheng, C. C., J. Pharm. Sci., 63, 307 (1974).

3. Bruylants, M. P., Bull. Soc. Chim. Belg., 36, 521 (1927).

4. Phillips, M. A., J. Chem. Soc., 2393 (1929).

5. Weinberger, L., and A. Day., J. Org. Chem., 24, 1451 (1959).

6. Getler, H., P. M. Roll, J. F. Tinker, and G. B. Brown, J. Biol. Chem., 178, 259 (1949).

7. MRI 2883-B Quarterly Progress Report No. 45, p. 13.

8. Raynolds, S., and R. Levine, J. Amer. Chem. Soc., 82, 472 (1960).

9. Langer, Jr., A. W., Trans. New York Acad. Sci., 27, 741 (1965).

10. Steck, E. A., L. L. Hallack, and A. J. Holland, J. Amer. Chem. Soc., 68, 129 (1946).

11. Gilman, H., and G. L. Schwebke, J. Org. Chem., 37, 4259 (1962).

12. Kaslow, C. E., and W. R. Clark, J. Org. Chem., 18, 55 (1953).

13. Cook, A. H., I. M. Heilbron, and L. Steger, J. Chem. Soc., 431 (1943) and references cited therein.

14. Dornfeld, C. A., and G. H. Coleman, Org. Syn. Coll. Vol. III, 701 (1955).

15. Barringer, Jr., D. F., G. Berkelhammer, S. D. Carter, L. Goldman, and A. E. Lanzilotti, J. Org. Chem., 38, 1933 (1973).

16. Barringer, Jr., D. F., G. Berkelhammer, and R. S. Wayne, Ibid, 38, 1937 (1973).

17. Baker, B. R., and F. J. McEvoy, Ibid, 20, 136 (1955).

18. Baker, B. R., F. J. McEvoy, R. E. Schaub, J. P. Joseph, and J. H. Williams, Ibid, 18, 153 (1953).

19. Jones, P. R. and J. R. Young, J. Org. Chem., 33, 1675 (1968).

20. Sato, T. and S. Watanabe, Chem. Comm., 515 (1969).

21. Brown, H. C., M. M. Rogic, and M. W. Rathke, J. Amer. Chem. Soc., 91, 4304 (1969).

22. Julian, P. L. and B. M. Sturgis, J. Amer. Chem. Soc., 57, 1126 (1935).

23. Balaspiri, L., B. Peuke, G. Papp, G. Dombi and K. Kovács, Helv. Chim. Acta, 58, 969 (1975).

24. Amstutz, E. D. and M. M. Besso, Ibid., 25, 1687 (1960).

25. Price, C. C. and R. M. Roberts, J. Amer. Chem. Soc., 68, 1204 (1946).

26. Steck, E. A., L. L. Hallock and A. J. Holland, J. Amer. Chem. Soc., 68, 380 (1946).

27. Leroux, Y., Bull. Soc. Chim. Fr., 359 (1968).

28. Obolentsev, R. D. and V. G. Bukharov, Khim. Sera-Org. Soedinenii Soderzhasheh v Nefti i Nefteprodukt., Akad Nauk SSSR., Bashkir. Filial, Doklardy 3-ei [Tret'ei] Nauch. Sessii, Ufa, 9 (1957); Chem. Abstr., 55, 25907i (1961).

29. Clemo, G. R. and G. A. Swan, J. Chem. Soc., 274 (1944).

30. Riegel, B., G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson, and R. H. Baker, J. Amer. Chem. Soc., 68, 1264 (1946).

31. Surrey, A. R. and R. A. Cutler, J. Amer. Chem. Soc., 68, 2570 (1946).

VII. PUBLICATIONS

Following is an up-to-date list of publications resulting from our work done in connection with the malaria study.

"3-Piperonylsydnone. A New Type of Antimalarial Agent," W. H. Nyberg and C. C. Cheng, J. Med. Chem., 8, 531-553 (1965).

"2,8-Bis(substituted amino)phenothiazine 5,5-Dioxides," P.-L. Chien and C. C. Cheng, J. Med. Chem., 9, 960-962 (1966).

"Structural Modification Studies of 3-Piperonylsydnone. I. Synthesis of Piperonyl-Substituted Pyrazoles, Isoxazoles, Triazoles, Oxadiazoles, and Thiadiazoles," S. G. Boots, and C. C. Cheng, J. Heterocyclic Chem., 4, 272-283 (1967).

"Synthesis and Antimalarial Evaluation of Some 1,7-Naphthyridines and 2,9-Diazaanthracenes," P.-L. Chien, and C. C. Cheng, J. Med. Chem., 11, 164-167 (1968).

"Pyrazoles I. Synthesis of 4-Hydroxypyrazolo[3,4-d]-v-triazine. A New Analog of Hypoxanthine," C. C. Cheng, R. K. Robins, K. C. Cheng, and D. C. Lin, J. Pharm. Sci., 57, 1044-1045 (1968).

"Pyrazoles II. Reactions of 1-Methyl-5-amino-4-pyrazolecarboxamide and Nitrous Acid. Introduction of a Nitro Group at Position 5 in the Pyrazole Ring," C. C. Cheng, J. Heterocyclic Chem., 5, 195-197 (1968).

"1,5-Naphthyridines: Synthesis of 7-Chloro-4-(4-diethylamino-1-methylbutylamino)-2-methoxy-1,5-naphthyridine and Related Compounds," D. J. McCaustland and C. C. Cheng, J. Heterocyclic Chem., 7, 467-473 (1970).

"Structural Modification of Febrifugine. Some Methylenedioxy Analogs," P.-L. Chien and C. C. Cheng, J. Med., Chem., 13, 867-870 (1970). ARPM

"Structural Modification Studies of 3-Piperonylsydnone. II. Synthesis of Piperonyl-Substituted Hydantoin, Thiohydantoin, Thiazolidinedione, Rhodanine, Imidazolinone and Related Compounds," W. H. Burton, W. L. Budde, and C. C. Cheng, J. Med. Chem., 13, 1009-1012 (1970).

"Structural Modification Studies of 3-Piperonylsydnone. III. Some Analogs of 3-Piperonylsydnone and 2,4-Diamino-5-piperonylpyrimidine," D. J. McCaustland, W. H. Burton, and C. C. Cheng, J. Heterocyclic Chem., 8, 89-97 (1971).

"Structure and Antimalarial Activity of Aminoalcohols and 2-(Chlorophenyl)-2-(4-piperidyl)tetrahydrofuran," C. C. Cheng, J. Pharm. Sci., 60, 1590-1598 (1971).

"Structure-Activity Relationship Studies on Antimalarial Phenanthrene Amino Alcohols. Modification of the Side Chain," P.-L. Chien, D. J. McCaustland, W. H. Burton, and C. C. Cheng, J. Med. Chem., 15, 28-33 (1972).

"Synthesis of Three ^{14}C-Labeled Phenanthrene Aminomethanols," P.-L. Chien and C. C. Cheng, Mikrochim. Acta, 401-412 (1973).

"Further Side Chain Modification of Antimalarial Phenanthrene Amino Alcohols," P.-L. Chien and C. C. Cheng, J. Med. Chem., 16, 1093-1096 (1973).

"Deaza Analogs of Some 4-, 6-, and 8-Aminoquinolines," D. J. McCaustland, P.-L. Chien, C. C. Cheng, J. Novotny, W. L. Schreiner, and F. W. Starks, J. Med. Chem., 16, 1311-1314 (1973).

"Novel Common Structural Feature Among Several Classes of Antimalarial Agents," C. C. Cheng, J. Pharm. Sci., 63, 307-310 (1974).

"A Structural Modification Study of the Antimalarial 2-(p-Chlorophenyl)-2-(4-piperidyl)tetrahydrofuran," D. J. McCaustland, P.-L. Chien, W. H. Burton, and C. C. Cheng, J. Med. Chem., 17, 993-1000 (1974). ARPM Publication No. 1226.

"Difference in Antimalarial Activity Between Certain Aminoalcohol Diastereomers," P.-L. Chien and C. C. Cheng, J. Med. Chem., 19, 170-172 (1976). ARPM Publication No. 1353.

"Structural Similarity between Febrifugine and Chloroquine," C. C. Cheng, J. Theoretical Biol., 59, 497-501 (1976). ARPM Publication No. 1343.

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