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SYNTHESIS OF ANTIMALARIAL AGENTS FROM 2,3-DIHYDRO-1,6-DIAZAPHEN--ETC(U)
JAN 79 J M COOK DAMD17-78-C-8003
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REPORT NUMBER FOUR

# SYNTHESIS OF ANTIMALARIAL AGENTS FROM 2,3-DIHYDRO-1,6-DIAZAPHENALENE DERIVATIVES

LEVEL II

Annual Summary Report

(for the period October 15, 1977 to December 31, 1978)

JAMES M. COOK

Department of Chemistry
University of Wisconsin-Milwaukee
Milwaukee, Wisconsin 53201







January 10, 1978

Supported By

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD17-78-C-8003

Department of Chemistry
University of Wisconsin-Milwaukee
Milwaukee, Wisconsin 53201

SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

## REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

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1,6-diazaphenalene, 5,8-diaminoquinoline analogs
9-methoxy-1,6-diazaphenalene,
4-methyl-5-nitro-6-methoxy quinoline
4-methyl-5-amino-6-methoxy quinoline

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

The investigation to date has centered on construction of the 9H-1,6-diazaphenalene (14a) system and the more important 9-methoxy derivatives. By use of the oxime and Semmler Wolff approach outlined in our original proposal, the 1,6-diazaphenalone (30) has been prepared, as well as the 5-amino quinoline derivative (29) depicted below. In addition, work toward the 9-methoxy analogs has progressed quite well (see intermediate 13' which has

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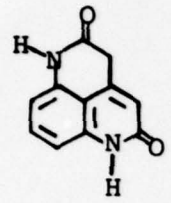
recently been prepared). Moreover, a two-step synthesis of dihydro-2,5-dihydroxy-1,6-diazaphenalene-1,6-dioxide (26) has been developed. The Semmler Wolff product (30) and the mono N-Oxide derivative of 26 have both been converted to 2,5-dichloro-1,6-diazaphenalene (39). The systems illustrated below will be converted to the diazaphenalene target compounds by standard methods during the second year.



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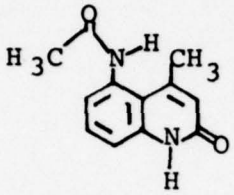

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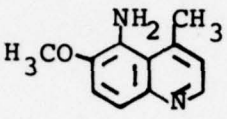

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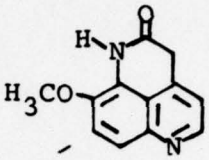

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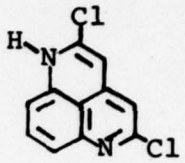

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# SYNTHESIS OF ANTIMALARIAL AGENTS FROM 2,3-DIHYDRO-1,6-DIAZAPHENALENE DERIVATIVES

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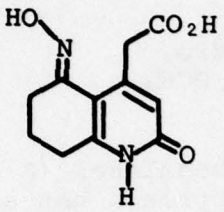
## SUMMARY

In agreement with the original synthetic plan, the 4-methyl-5-oxo-2-quinolone acetic acid derivative and 4-methyl-5-oxo-2-quinoline were converted to the corresponding oximes (20) and (28), respectively.



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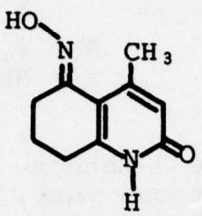

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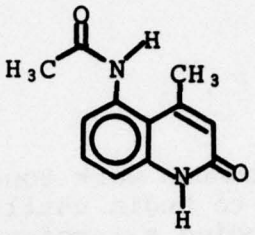

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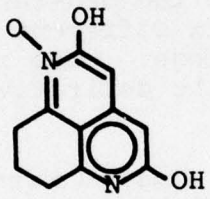

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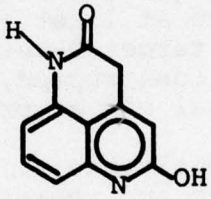
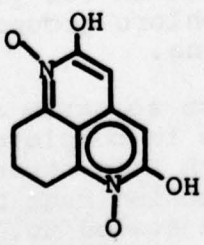


30

Treatment of the 4-methyl oxime (28) under Semmler Wolff conditions provided the desired 4-methyl-5-amino-2-quinolone derivative (29). The 5-oximino-4 acetic acid derivative (20) was converted to the key, quinolone N-oxide (21) by treatment with either heat or acid. When this N-oxide (21) was subjected to modified Semmler Wolff conditions, aromatization occurred to provide the important 2,5-dihydroxy-1,6-diazaphenalene (30); this is the first entry into this ring system and is certainly one of the principal goals of the first year of work. However, even more important reactions have been developed. A two-step synthesis of the dihydro-2,5-dihydroxy-1,6-diazaphenalene-1,6-dioxide (26) has been carried out in very good yield; this intermediate is expected to provide even better yields of 30 on further work.



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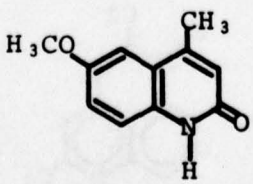

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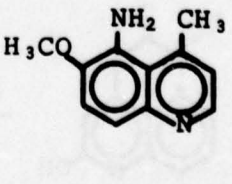

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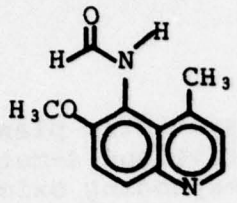

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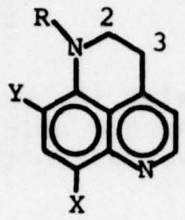
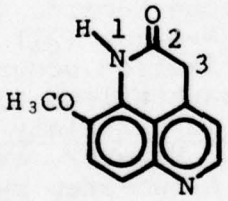


A or B

A = 2,3 dihydro,
X = NHR, Y = $OCH_3$

Although work toward the 9-methoxy diazaphenalenes (A or B) was not to begin until the second year, this approach has already been studied extensively. The 4-methyl-6-methoxy-2-quinolone (3) has been converted in three steps to the key amine, 4-methyl-5-amino-6-methoxy-quinoline (8) and to the 5-N-formyl derivative (12). There are at least five or six different methods to convert 8 or 12 to the target 9-methoxy analogs. Once the parent ring structures are constructed, all of the derivatives outlined in our original proposal can be prepared.

Quite recently the amine 8 was stirred with 2 moles of lithium diisopropylamine and poured onto carbon dioxide. The dianion had formed and the product of this reaction was purified. The spectral and analytical data are in complete agreement with the structure of the 9-methoxy-diaxaphenalone (13') depicted below. This reaction must now be scaled up to practical levels.



13'

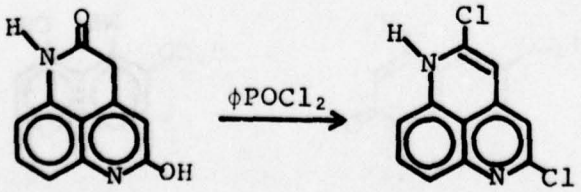
$M^+$ at 214 (90), 199 (100), 185 (2), 181 (4), 171 (40).

$199 = M^+ - 15$

$171 = M^+ - 15 - 28$

Ir (KBr) 1640, 1620, and 1590 $cm^{-1}$.

The extremely important conversion of the diazaphenalone (30) to 2,5-dichloro 1,6-diazaphenalene (39) was carried out in 88% yield by heating 30 in phenyl phosphonic dichloride. The chloro groups were subsequently removed to generate 1,6-diazaphenalene.

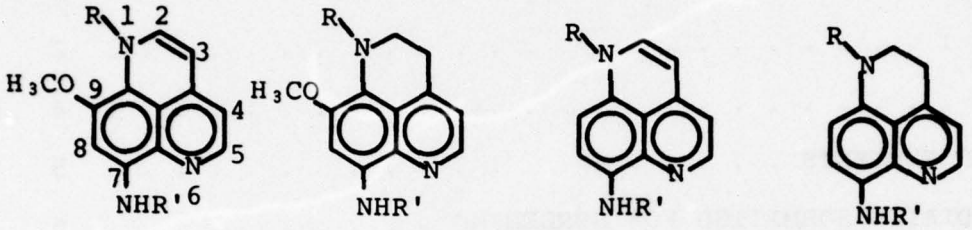


30 39

Mass spectrum and NMR are in complete agreement with this structure. Reaction must be repeated and scaled up.

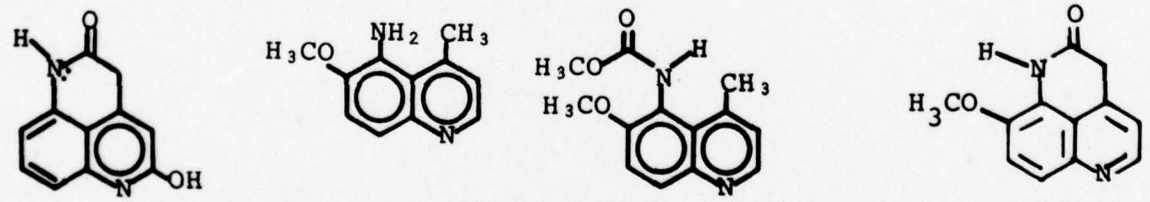
## FORWARD

The following report concerns research directed toward the synthesis of potential antimalarial agents, based on the structures of 9-methoxy and 9-H-7-alkylamino-1,6-diazaphenalene bases (A, C) and their 2,3-dihydro analogs (B, D); the resemblance to 5,8-diaminoquinolines, however, is not accidental.




A B C D

Although the original proposal was written to cover a three year period, investigations have been conducted associated both with synthesis of the more important 9-methoxy compounds (A and B) as well as the 9-H analogs (C and D) rather than waiting for the second year to investigate the 9-$OCH_3$ analogs. Consequently, preparation of the active target molecules hoped for in the first year has not been completed; however, the program is still somewhat ahead of schedule for entry into the 9-H diazaphenalene ring system (30) has been completed, while the key intermediates 12 and 13' for the 9-$OCH_3$ derivatives have also been prepared.



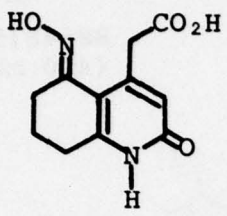

30* 8 12 13'

The report is not written in chronological order, in an historical sense, but the most important results are presented first. The synthesis of the 4-methyl-5-amino-6-methoxy quinolines are described, followed by discussion of entry into the key 1,6-diazaphenalene (30*) by the route described in our original proposal (oxime formation, followed by a Semmler Wolff "type" rearrangement). The scaleup of reactions which led to the preparation of 5-oxo-5,6,7,8-tetrahydrocoumarin-4-yl acetic acid, the starting material for compounds such as 30* will be presented, followed by a list of reactions which were attempted but proved unproductive and also future proposals. The last section of the report is the experimental section.

# TABLE OF CONTENTS

A.

1. Intermediates sent for screening whose structures have been unambiguously assigned (see report). No significant antimalarial activity has been found in the intermediates screened to date.



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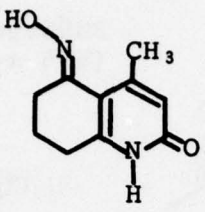

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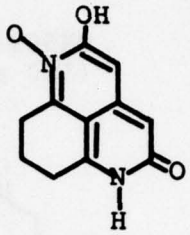

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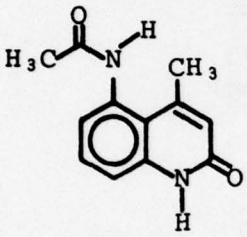

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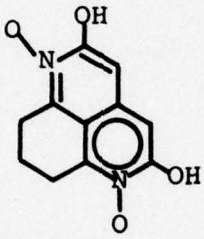

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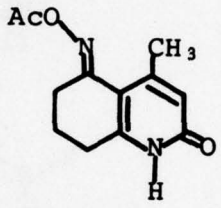

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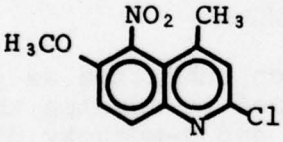

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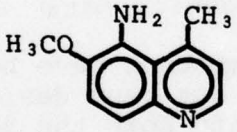

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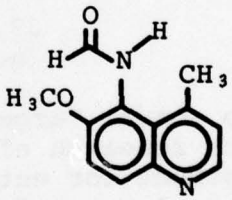

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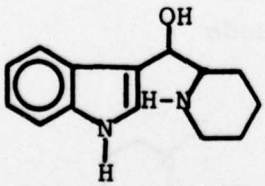

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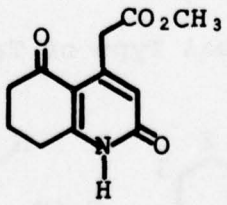

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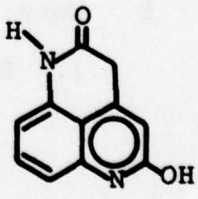

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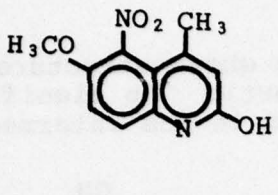

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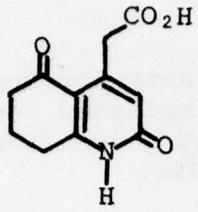

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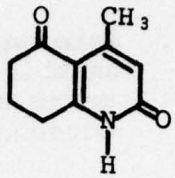

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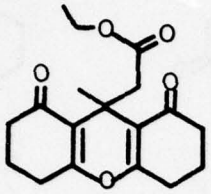

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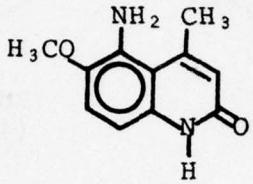

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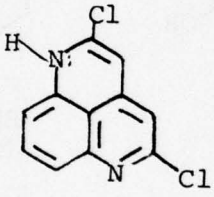

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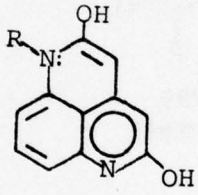
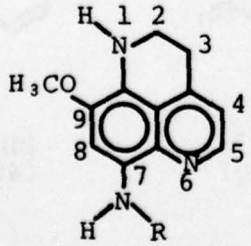


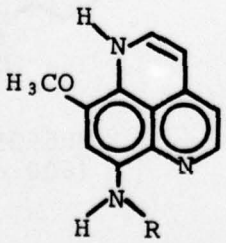
R=H
BH81638

2. No actual target compounds have been submitted as yet. The research effort has been designed to develop the best methods for entry into both the 9H and 9-methoxy diazaphenalenes before preparation of derivatives is begun.

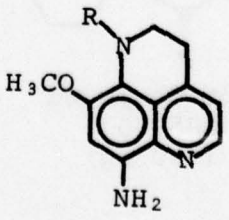
B. Work in Progress:

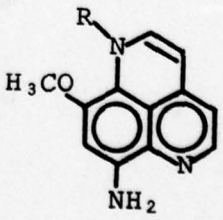
1. Eventual Type of Target Compounds





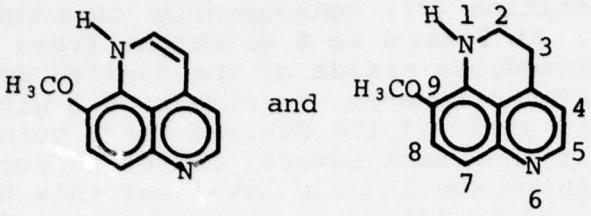
A, R = antimalarial effective sidechain





B, R = antimalarial effective sidechain

Initial Targets:



13a and 13b

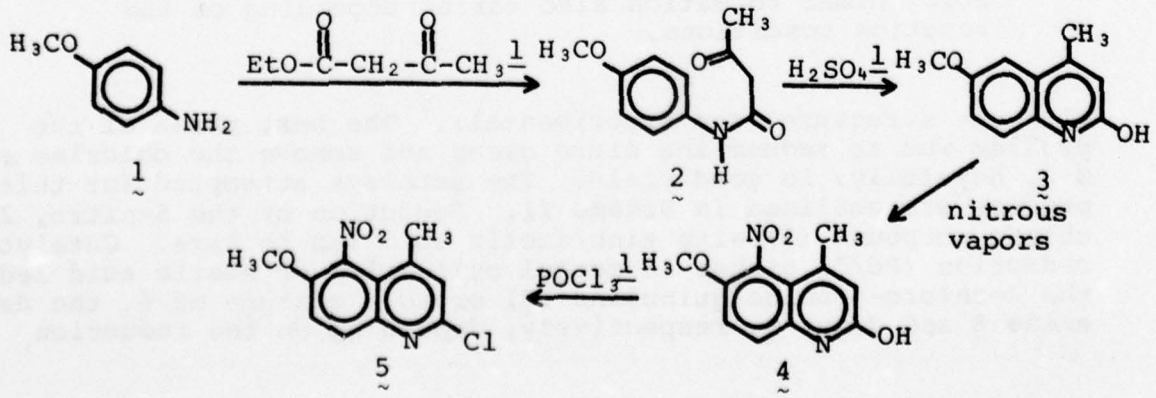
These two systems can be nitrated to provide the 7-nitro analogs *via* trivial reactions, followed by reduction to the amines.

In the original three-year plan (contract), it had been proposed to prepare the 9-H diazaphenalene analogs first and then to develop methodology to attach the 9-$OCH_3$ group, which is necessary for higher activity, in the second year of the contract. However, we have decided to work toward the 9-H analogs *via* our previous oxime approach, but also to combine classical and modern synthetic methods to prepare the 9-methoxy analogs at the same time. In actuality we are therefore ahead of schedule as regards our overall plan.

The work toward the 9-methoxy diazaphenalene derivatives carried out to date is outlined in Schemes I-IV. Initial entry into the desired quinoline ring system (3) was completed by following the work of Elderfield, Campbell, and coworkers. Reaction of p-anisidine (1) with ethyl acetoacetate provided the amide (2) in good yield which was cyclized by treatment with sulfuric acid analogous to the published work (1). The task of converting the 2-hydroxy-4-methyl-6-methoxy quinoline (3) to the

Scheme I

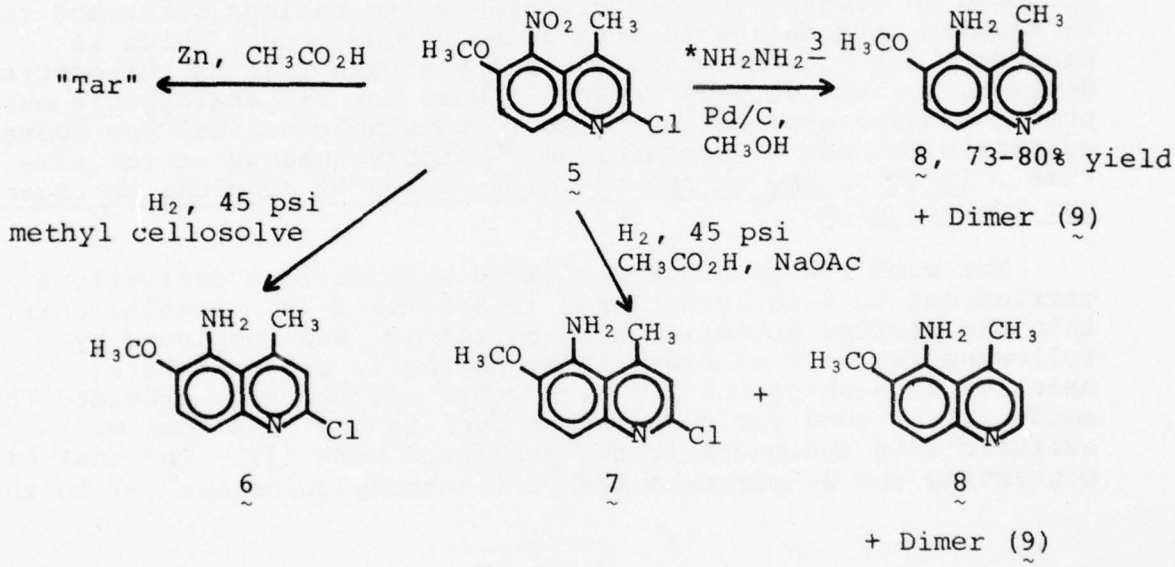
Preparation of 2-Chloro-4-methyl-5-nitro-6-methoxy Quinoline (5)



5-nitro derivative was not straightforward. Reports in the literature have shown that the 6-methyl analog of 3 can be nitrated in the 5-position (2); consequently, this approach appeared attractive. At least 4 to 6 different types of nitration reactions were attempted, but yields of the 5-nitro derivative (4) were low or non-existent; however, treatment of 3 with nitrous vapors (3) gave a 90% yield of the desired nitro quinolone (4) on a two gram scale. It then took several months to successfully scale the reaction above the 10 gram level but this has now been done. The nitro quinolone (4) was converted to the 2-chloro-4-methyl-5-nitro-6-methoxy quinoline (5) by standard methods ($POCl_3$) (1). The NMR, ir, and mass spectrum of 5 are in complete accord

Scheme II

Preparation of Pure 4-Methyl-5-amino-6-methoxy Quinoline (8)




*In the hydrazine reduction the amount of dimer formed was very small under the conditions developed by Weber (see Experimental). In the reduction carried out in acetic acid, dimer formation also varied depending on the reaction conditions.

with the structure (see Experimental). The next phase of the problem was to reduce the nitro group and remove the chlorine atom at C-2, hopefully, in good yield. The pathways attempted for this process are outlined in Scheme II. Reduction of the 5-nitro, 2-chloro compound (5) with zinc/acetic acid led to tars. Catalytic reduction (Pd/C) either in methyl cellosolve or acetic acid led to the 2-chloro-5-amino quinoline (6) or to a mixture of 6, the desired amine 8 and dimer 9, respectively, depending on the reduction

conditions. However, treatment of 5 with hydrazine and Pd/C (4) led to excellent (73-80%) yields of the desired 4-methyl-5-amino-6-methoxy quinoline (8); this reaction has been scaled up to the 10 gram level.

The 4-methyl-5-amino-6-methoxy quinoline is the key intermediate for preparation of the 9-methoxy-1,6-diazaphenalenes and can now be prepared quite easily. The hydrazine method not only removed the chlorine atom but also reduced the 5-$NO_2$ group in the same step (see Future Proposals for the importance of this compound).

In order to ensure that a strong base, such as lithium diisopropyl amide would form a carbanion at the 4-methyl function of a 6-methoxy quinoline, the experiment outlined in Scheme III has been carried out. Following the work of Uskokovic (5) and Wolfe *et al.* (6), the 4-methyl-6-methoxy derivative 10 was treated at low temperature in tetrahydrofuran with LDA followed by quenching of the anion with carbon dioxide. The quinoline-4-acetic acid (11) was produced in excellent yield and this adds support for the types of reactions we are now employing to close the third ring, some of which are outlined in Scheme IV. In addition, the nitration of a derivative such as 11 in the 5-position is also possible and would eventually lead to 9-methoxy diazaphenalenes (see Future Proposals).

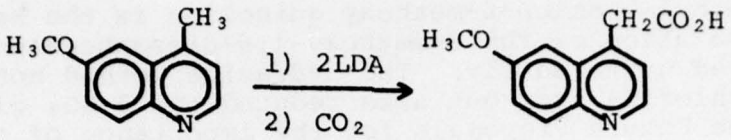
The amine 8 (see Scheme II) was converted in excellent yield to the N-formyl compound 12 (Scheme IV) by treatment of 8 with formic-acetic anhydride (7). We have wanted the formyl compound 12 because of the possibility of effecting a Madelung (8) "type" condensation between the formyl group and the methyl group located *peri* to each other in 12. The Madelung (8) indole synthesis has been employed to form five membered rings; however, examination of models would seem to indicate the cyclization to the six membered ring would occur easily in our case, especially since the two reactive groups are located *peri* to one another.

Since we have had the formyl compound in our hands for a short time, only three reactions have been done and they are outlined in Scheme IV. Treatment of 12 with t-butoxide in hot t-butanol gave only the amine 8. None of the desired diazaphenalene 13 was formed. Furthermore treatment of 12 with LDA at low temperature also gave no reaction. It was felt LDA is too bulky a base to attack this position or that the formyl derivative is *anti* to the methyl carbanion in 12 so that cyclization has not taken place. If this is true these complications can be circumvented via use of $KNH_2$ as the base or by forcing the formyl group into a *syn* relationship to the 4-methyl group of 12. Methodology for this is outlined at the bottom of Scheme IV.

One more attempt bears special mention: heating a mixture of 12 and potassium t-butoxide (neat) to 250° behaved similarly to Madelung condensations reported in the literature *vis a vis* physical behavior and appearance. This product must be purified to determine

Scheme III

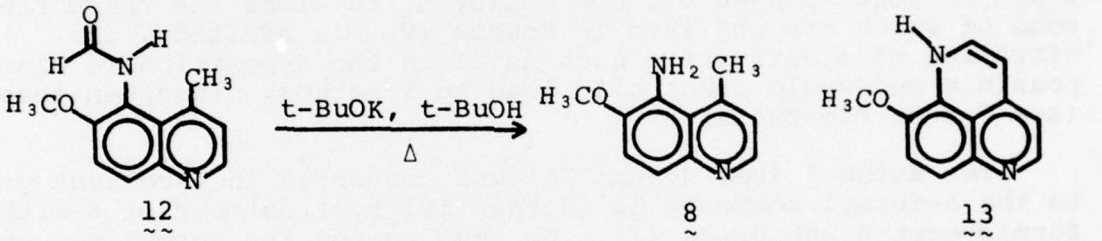
Investigation of the Carbonylation Reactions of the 4-Methyl Group of 4-Methyl-6-methoxy Quinoline (10)




10 11

Scheme IV

Attempted Cyclization of the Formamide 12 via Madelung "Type" Reaction Conditions*



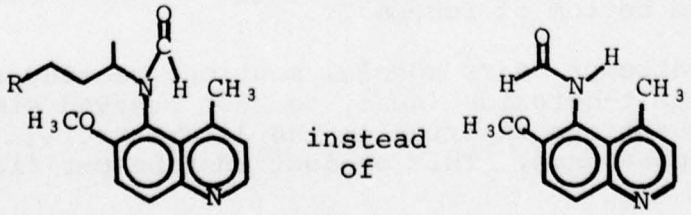

12 8 13

None of this was formed.

12 —(2LDA/THF, -30°)→ No Reaction

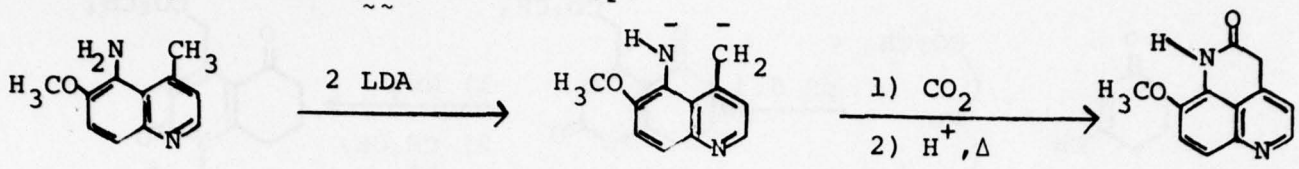
12 —(t-BuOK (neat), 250°)→ Mixture of Products (Chromatography to clean up this reaction must be completed.)

*Only three experiments have been carried out and many more must be done until the correct reaction conditions are determined. At present we feel that 250° is too hot. Also, the N-H function of the formamide should probably be alkylated to force the formyl group closer to the methyl function, as illustrated below:



if any of 13 is present.

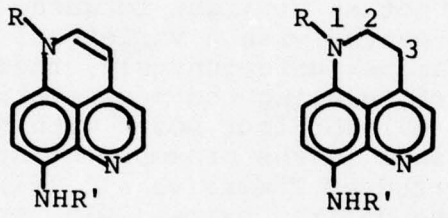
The most important result in the 9-methoxy series was recently achieved in our labs by Mr. Weber. The dianion of 8 was formed by treatment of 8 with two moles of LDA, and subsequently quenched with carbon dioxide. The carboxy derivative cyclized to the desired diazaphenalone (13') on work up.




8 13'

This procedure must be scaled up (See Future Work)

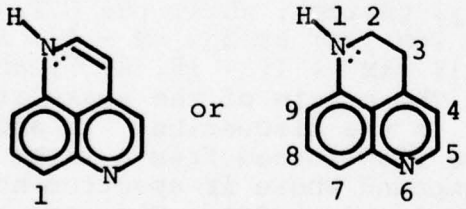
2. Eventual Target Compounds (9H analogs)



C D

R = H or antimalarial active sidechain
R' = H or antimalarial active sidechain

Initial Target (Parent Ring System)



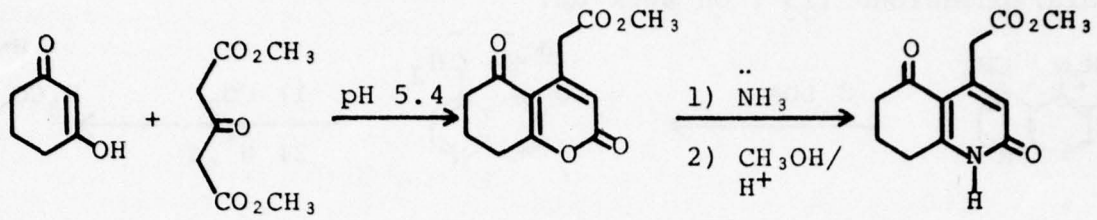
14a or 14b

The initial targets can be nitrated in the 7 position, reduced and alkylated to provide the derivatives listed above.

a. Entry into Dihydro Tricyclic Diazaphenalene Derivatives

Early during the investigation of the reaction of dicarbonyl compounds with dimethyl β-ketoglutarate, it was found that stirring a solution of cyclohexane-1,3-dione (15) in citrate-phosphate buffer (9) with dimethyl β-ketoglutarate (16) provided a very good yield of the 5-oxo-4-alkyl-5,6,7,8-tetrahydrocoumarin (17), as illustrated in Scheme V. The oxocoumarin appeared to be an excellent precursor for the tricyclic system, for replacement of the 1- and 5-oxo functions with nitrogen atoms might well provide the basic skeleton of 14a or 14b.

Scheme V

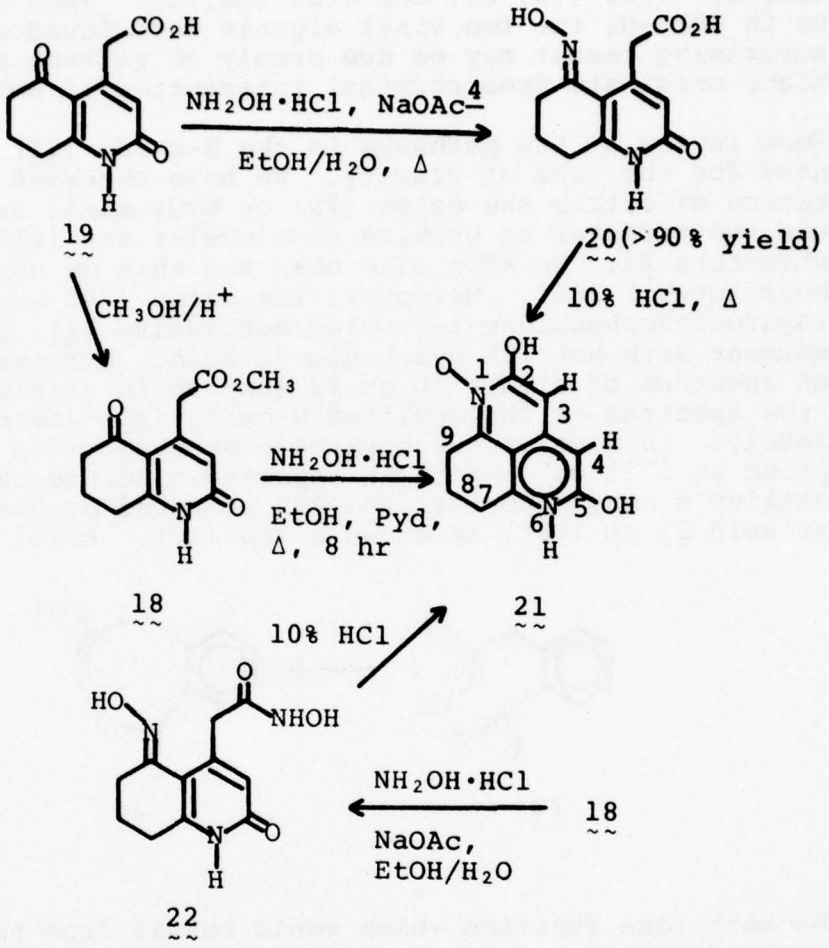



15 16 17 18

Conversion of the 5-oxocoumarin (17) to the 5-oxo-4-alkyl-5,6,7,8-tetrahydro-2-quinolone (18) was carried out by published methods (9,10) in 90% yield (see Scheme V); but, addition of the second nitrogen function was not as straight-forward. The 5-oxoquinolone ester (18) was reacted with a variety of amines including ammonia and benzylamine; unfortunately, these attempts ended in failure. In contrast, heating the 5-oxo-tetrahydroquinolone acetic acid derivative (19) for four hours with hydroxylamine hydrochloride in aqueous ethanol in the presence of sodium acetate, analogous to conditions reported by Tamura *et al.* (11), provided a 96% yield (Scheme VI) of the desired oxime (20): mp 226-230°(dec); ir (KBr) 3310, 2860, 1702, 1642, 1598, 955, and 938 $cm^{-1}$. The presence of the carboxyl function and the bands at 955 and 938 (oxime) (11) in the infrared spectrum of the yellow solid supported the structure of the oxime (20). The NMR spectrum in $D_2O$, NaOD contained signals at δ 1.82 (2H, m), 2.61 (4H, m), 3.80 (2H, s, $-CH_2-$) and 6.18 (1H, s, vinyl proton), while the C.I. mass spectrum ($NH_3$) had a parent ion (1%) at 237 (M + 1); furthermore intense peaks occurred at 219 [$(M^+ + 1) - 18, H_2O$)] and 203 [$(M^+ + 1) - H_2O - 16$ (0)]. The origin of the peaks at 219 and 203 will become clear later in the discussion. In addition, the oxime (20) when heated above 226° turned from a light yellow solid to a yellow-orange compound whose ir spectrum no longer resembled that of the original oxime (20). The same oxime (20) was obtained when 19 and $NH_2OH \cdot HCl$ were heated in a pyridine/ethanol solution for several hours (no NaOAc added); but, when the 5-oxoquinolone ester (18) and $NH_2OH \cdot HCl$ were heated in an ethanol-water solution for several hours the major product was not the oxime (20) but the yellow colored oximino hydroxamic acid (22) (mp > 300°); ir (KBr) 3100-2300 (broad bands), 1640, 1620, 1588, 1516, 1422, 1170 (955 and 980 oxime) $cm^{-1}$ (4). The carboxyl function was absent in the spectrum of 22 as compared to that of 20 while elemental analysis clearly indicated the molecule contained three nitrogen atoms. All attempts to obtain a mass spectrum led to an ion at *m/e* 218 which was not the parent peak (see below).

However, both the oxime (20) and the hydroxamic acid (22) gave the same yellow-orange solid when treated with hot 10%

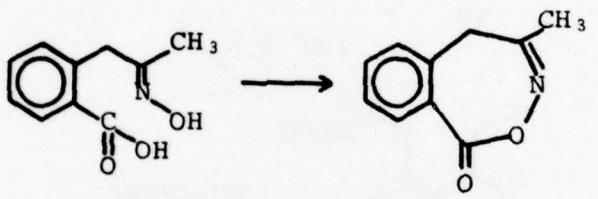
Scheme VI




hydrochloric acid. Furthermore, the ir spectrum of this solid was identical to that obtained earlier, when a small amount of 20 was heated to 226° in a capillary tube. In addition, prolonged heating of the 5-oxoquinolone methyl ester (18) with hydroxylamine hydrochloride in an ethanol-pyridine solution provided the same yellow-orange precipitate (21) directly. The structure of this yellow-orange solid was proven, unequivocally, to be that represented by structure 21. This high melting solid (mp > 350°) had a molecular ion at 218 mass units (E.I. and C.I. spectra); furthermore the base peak in the C.I. spectrum occurred at $M^+ - 16$ characteristic for the loss of oxygen from N-oxides (12); similar results were seen in the electron impact spectrum. The ir spectrum contained bands at 3400, 3040 (OH) and 1620 (pyridone C=O), furthermore strong signals were found at 1595, 1290, and 1180 $cm^{-1}$ characteristic of absorptions from N-oxides observed in similar environments (13). Although 21 was insoluble in most organic solvents, NMR spectra could be obtained both in trifluoroacetic acid and $D_2O$ (NaOD) solution: $\delta$ ($CF_3CO_2H$), 2.48 (2H, m), 3.56

(4H, two overlapping triplets), 6.95 (1H, s, vinyl), and 7.00 (1H, s, vinyl proton); δ ($D_2O$, NaOD), 2.20 (2H, m), 2.94 (2H, t), 3.20 (2H, t), 6.05 (1H, s), and 6.20 (1H, s). When the spectrum was run in DMSO-$d_6$ the two vinyl signals were found at δ 5.94; this surprising result may be due simply to solvent shifts, or in fact might originate from chemical interaction of DMSO with 9 (14).

Some review of the pathways to the N-oxide (21) should be presented for the sake of clarity. We have observed the consistent cyclization of either the oxime (20) or hydroxamic acid (22) in the mass spectrometer to provide a molecular ion (218) consistent with structure 21. We have also observed this on heating 20 or 22 to temperatures > 226°. Moreover, the oxime (20) was converted to the dihydrodiazaphenalene-1-N-oxide derivative (21) in 96% yield on treatment with hot 10% hydrochloric acid. Furthermore, when the NMR spectrum of either 20 or 22 was run in trifluoroacetic acid, the spectrum of the cyclized N-oxide (21) was observed, immediately. In none of our work have we observed a carbonyl absorption at 1721 $cm^{-1}$ which is reported (13c) to be present in "Gottlieb's anhydroderivative, 24" produced by heating the oximino acid 23 at 175°, as shown below (15). Also, the signal



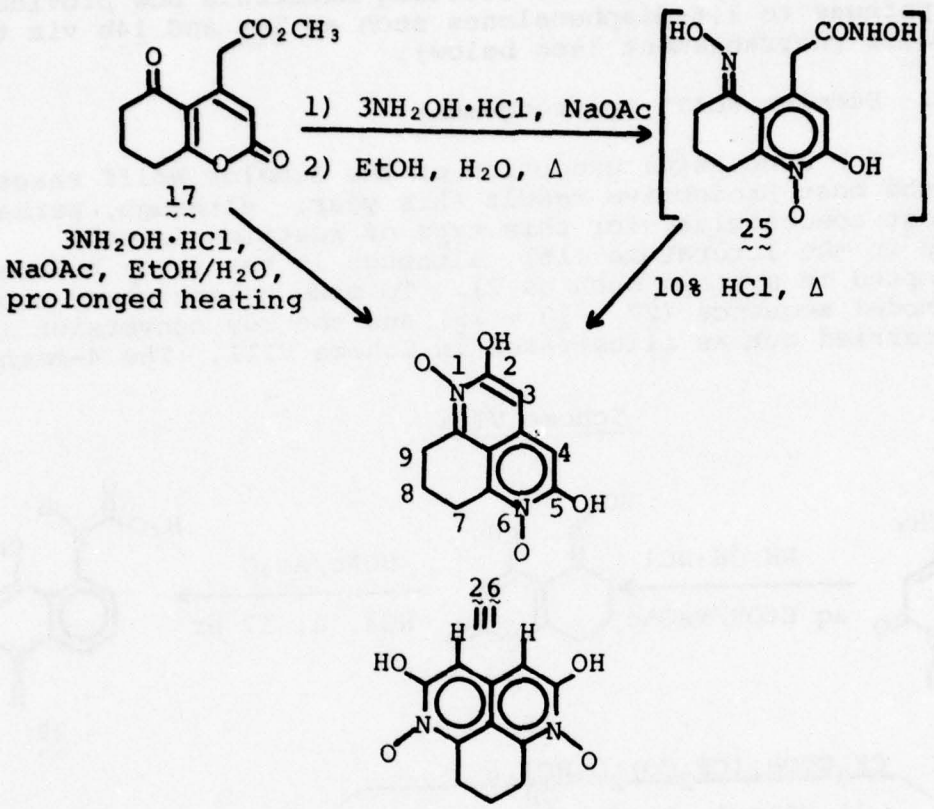

23 24

for the methylene function which would result from this attack studied by Gottlieb and later reinvestigated by Moriconi (13c) was absent from the NMR spectrum of 21. Apparently the peri position of the oxime (20) is perfectly set up for the desired cyclization to take place in the case of 20 or 22.

It is obvious that acidic conditions are required to force bases 18, 20, and 22 to cyclize to the N-oxide 21; however, the yields are quite high in all these conversions (transformation of 19 to 21 can be carried out in better than 80% overall yield).

Although the yield of the diazatricyclic system (21) from 19 was good, it was felt a shorter route might be developed if better use was made of the 5-oxo-4-alkyl-5,6,7,8-tetrahydrocoumarin (17). To this end the two-step synthesis of the key tricyclic ring system (26) has been developed as outlined in Scheme VII. Reaction of 15 with 16 gave 17 in good yield, as described before. The 5-oxocoumarin derivative was then heated with three moles of hydroxylamine hydrochloride in aqueous alcohol; prolonged heating, with further addition of $NH_2OH \cdot HCl$ to the mixture, provided an

Scheme VII




88% yield of the dihydro-2,5-dihydroxyl-1,6-diazaphenalene-1,6-dioxide (26), while heating the same solution for only 10 hours furnished a mixture of 26 and another compound felt to be the intermediate hydroxamic acid (25). The mixture of 25 and 26 was converted quantitatively to 26 on treatment with hot 10% hydrochloric acid.

The physical and spectral data are in complete agreement with the structure of 26. The orange colored solid which has a high melting point (>300°), characteristic of similar quinolones was insoluble in most organic solvents. The chemical ionization mass spectrum ($NH_3$) showed successive losses of 16 (0) at 219 and 203 mass units, respectively, confirming the bis-N-oxide nature of 26 (12). In addition, ir (KBr) bands were found at 3450 (OH), 3050, 1630 (C=O), 1610, 1295, and 1185 $cm^{-1}$; the strong bands at 1610, 1295, and 1185 are due to $C=N^+-O^-$ and $N^+-O^-$ stretching vibrations characteristic of pyridine and pyridine-N-oxides (13). The symmetrical character of the diazaderivative (26) was clearly shown by its NMR spectrum ($CF_3CO_2H$) which contained only three signals: $\delta$ 2.52 (2H, m, C-8H's), 3.62 (4H, t, $J$ = 6 Hz, C-7, and

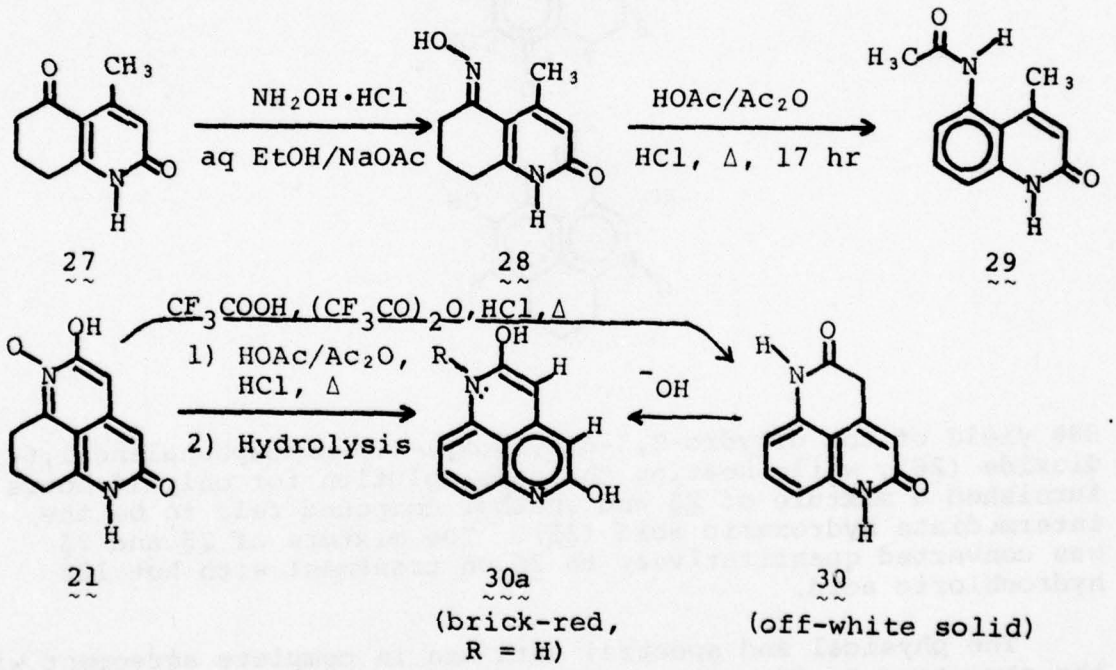
C-9H), and 7.00 (2H, s, C-3 and C-4, vinyl protons).

The simple synthesis of the dihydrodiazaphenalene derivatives 21 and 26 from readily available starting materials now provides a facile pathway to 1,6-diaphenalenes such as 14a and 14b via the Semmler Wolff rearrangement (see below).

b. Semmler Wolff Rearrangement

The successful execution of the Semmler Wolff reaction has been the most productive result this year; although, perhaps not the most spectacular, for this type of reaction is well documented in the literature (16), although it has never before been attempted in systems such as 21. To make a long story short, both the model sequence (27 → 28 → 29) and the key conversion (21 → 30) were carried out, as illustrated in Scheme VIII. The 4-methyl-

Scheme VIII




27 28 29

21 30a (brick-red, R = H) 30 (off-white solid)

5-oxo-tetrahydro-2-quinolone (27) was prepared by thermal decarboxylation of the acid 19 (see Scheme VI) in 90% yield and was converted to the oxime 28 by standard methods. When 28 was heated in acetic anhydride/acetic acid in the presence of anhydrous hydrogen chloride for one hour the oxime O-acetate of 28 was produced; however, prolonged heating of 28 under analogous conditions provided a 53% yield of the 5-amino-2-quinolone (29). The structure has been confirmed by ir, NMR, mass spectroscopy and CHN analysis (see Experimental).

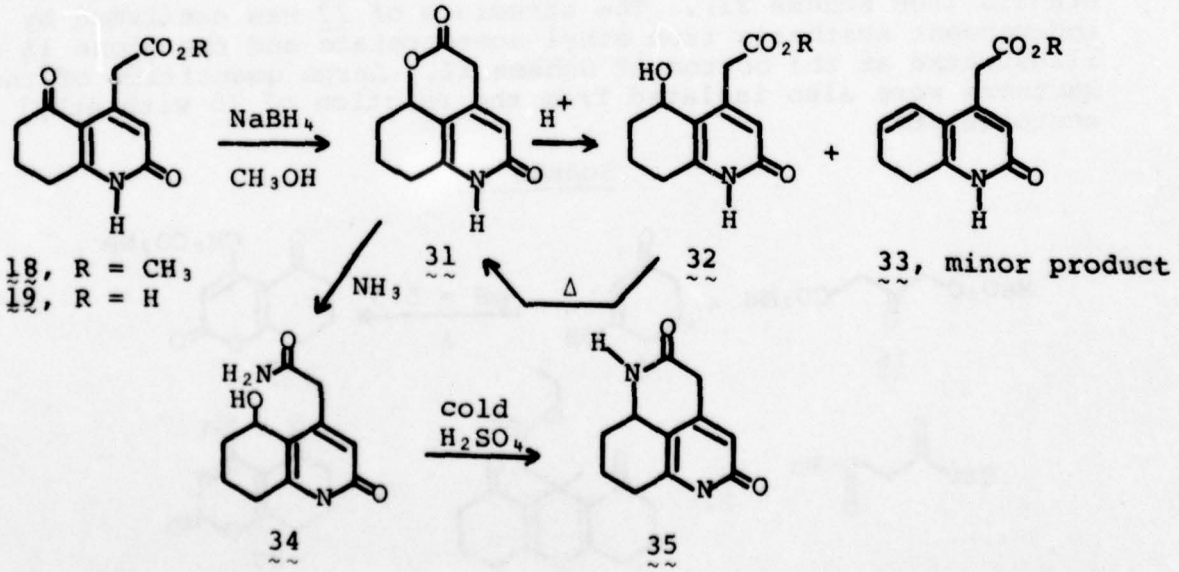
Even more exciting was the conversion of the N-oxide 21 into the target diazaphenalene ring system 30 [R = $C(O)CH_3$, or R = H after hydrolysis]. The proton NMR spectrum of 30a (R = H) contained signals only in the aromatic region, except for the two broad OH resonances which appeared at very low field (see Experimental). The ir, mass spectrum and elemental analysis fully support the structure of 30a. This experiment appears to work even better in the case of 21 when trifluoroacetic acid, trifluoroacetic-anhydride and HCl are employed to give 30 in greater than 88% yield.

This work in Scheme VIII was a pivotal conversion outlined in our original proposal and has been successfully completed. We have now removed the OH groups from 30 via standard methods ($POCl_3$, or $\phi POCl_2$, followed by reduction) and must now convert the parent diazaphenalene into useful antimalarial agents.

c. Lactone Approach

Another approach to the 9H analogs 14a and 14b has also been pursued and is outlined in Scheme IX. The 5-oxo derivatives 18 or 19 were treated with sodium borohydride to provide the lactone (31), the alcohol (32), and the alkene were hydrolysis products. The lactone was treated with ammonia which gave the amide 34 and this amide was dissolved in cold concentrated sulfuric acid to effect solvolysis of the alcohol which could be quenched by the weakly basic nitrogen atom. A white solid has been isolated from this sequence which may be the lactam (35) but insufficient evidence, in terms of spectroscopy, at this point makes this assignment (35) very tentative. Work is in progress at present to attempt to correlate the structure of this lactam with the N-oxide 21.

Scheme IX




18, R = $CH_3$
19, R = H

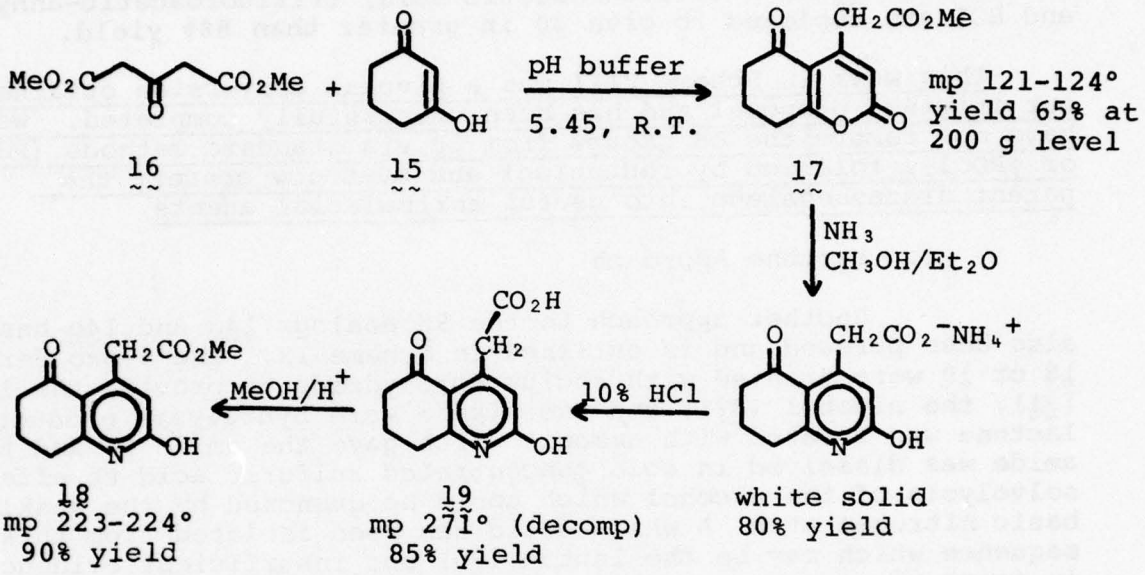
31 32 33, minor product

34 35

d. Scaleup Work

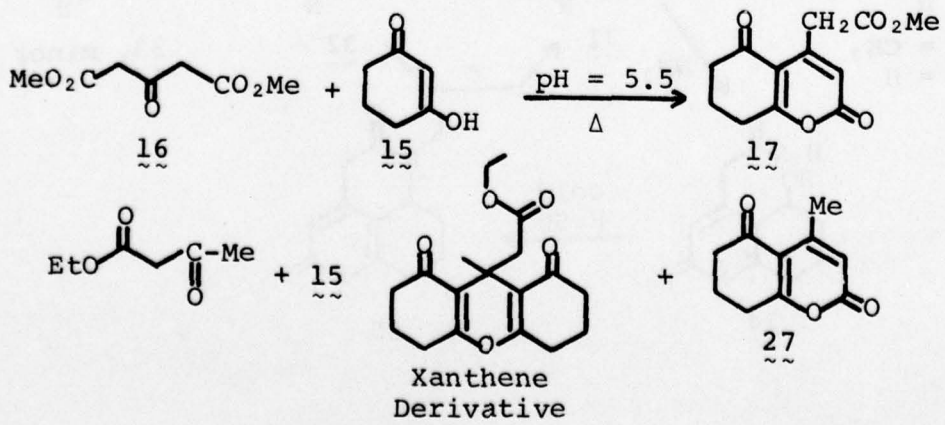
The scheme developed in this laboratory to prepare 4-alkyl-5-oxo-5,6,7,8-tetrahydrocarbostyrils has been scaled up to the 200 g level (Scheme X).

Scheme X

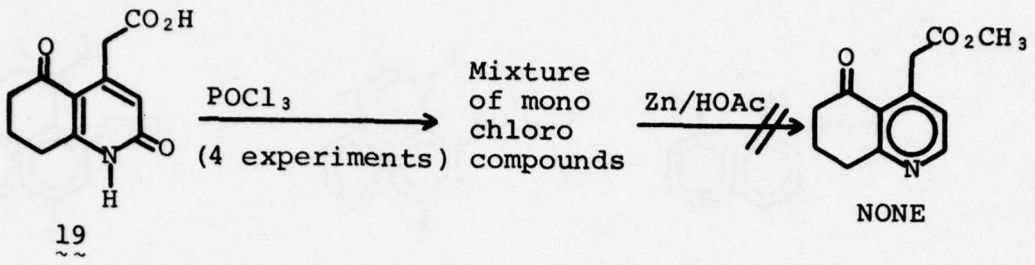



The reaction of cyclohexane-1,3-dione with dimethyl β-ketoglutarate to provide the 5-oxo-5,6,7,8-tetrahydrocoumarin 17 takes several weeks to complete when carried out at room temperature. Conditions to increase the reaction rate were tried including the use of heat; unfortunately, considerable quantities of 4-methyl-5-oxo-5,6,7,8-tetrahydrocoumarin 27 were formed under these circumstances (see Scheme XI). The structure of 27 was confirmed by independent synthesis from ethyl acetoacetate and the dione 15 as illustrated at the bottom of Scheme XI. Large quantities of the xanthene were also isolated from the reaction of 15 with ethyl acetoacetate.

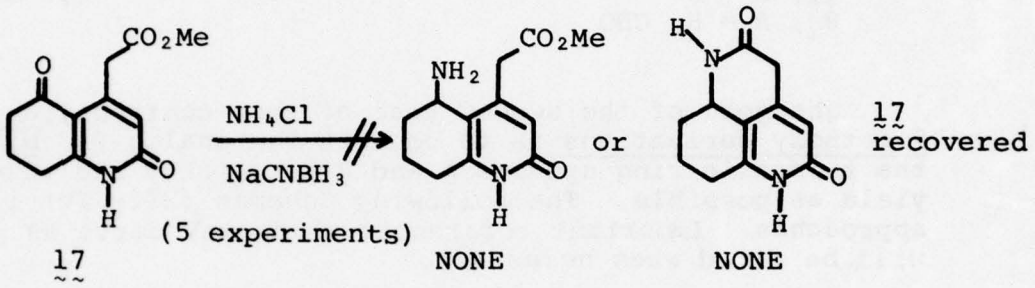
Scheme XI



e. Reactions that Proved Unproductive

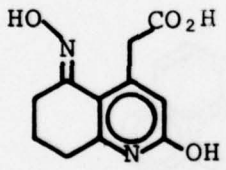



19




17

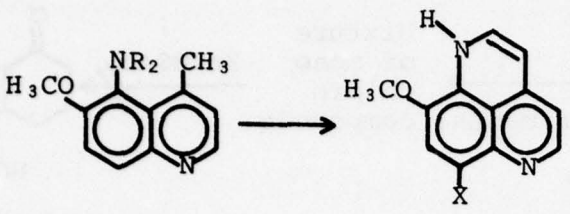
To try to characterize 20 (early in the research problem) the following reactions were attempted. We were quite uncertain of the structure of 20 at that time.




20

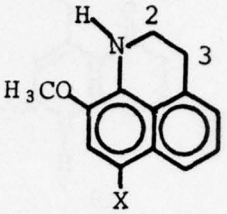
| | | |
|---|---|---|
| | $\xrightarrow[CH_3CO_2H]{Zn\ dust}$ | Solution turns brick red. New tarry material too difficult to characterize. |
| 20 | $\xrightarrow[CH_3OH]{NaBH_4/}$ | No reaction. No contact with 20. |
| 20 | $\xrightarrow[THF]{LiAlH_4}$ | Some reaction. Reaction mixture is a gummy oil. Work dropped in lieu of better results in other areas. |

## Future Research Toward 9-Methoxy Diazaphenalenes (A) and (B)
## Second Year Plan




8a, R = H
8b, R = O
8c, R = H, CHO

A

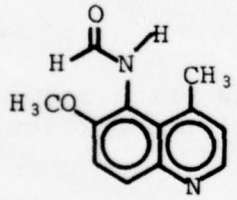



B
2,3 dihydro

The goal of the second year of this contract, as regards the 9-methoxy derivatives is to convert the analog 8a, b, or c into the tricyclic ring systems A and B as quickly and in as high a yield as possible. The following Schemes (XII-XIV) illustrate our approaches. Important references which may serve as precedents will be cited when necessary.

### Scheme XII

Madelung Approach (8)



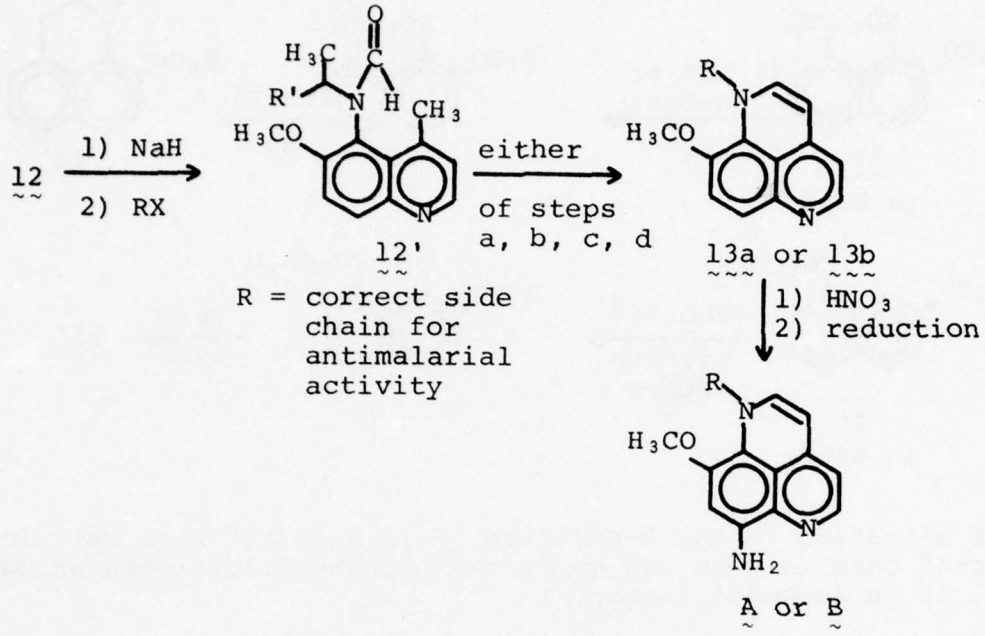

a) 12 —(2 1/2 eq lithium diisopropyl amide)→ 13

b) 12 —(*t*-BuOK, Δ, 250°)→ 13

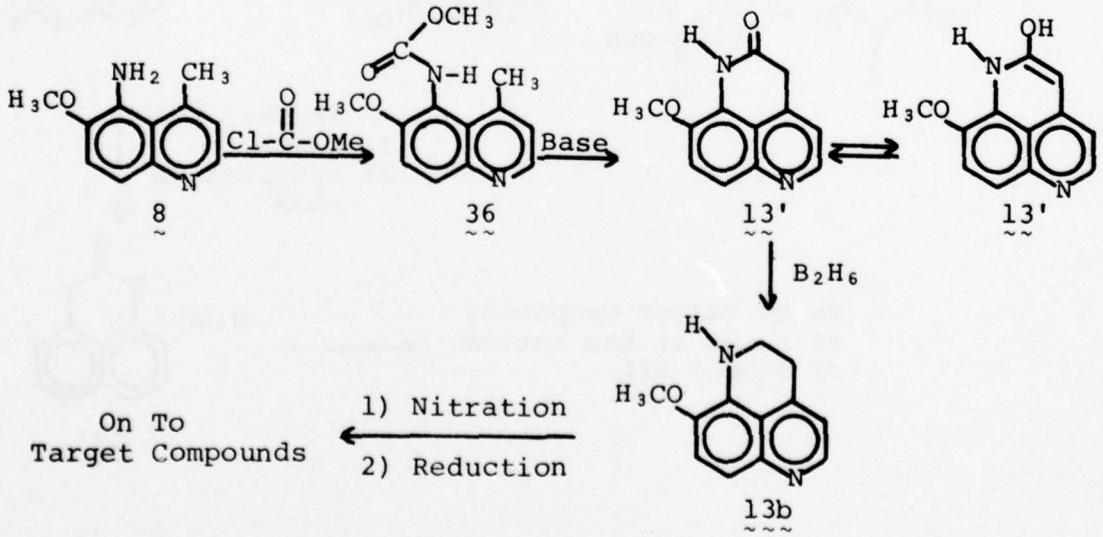
c) 12 —($2KNH_2$)→ 13

d) 12 —(other bases)→ 13

If the formyl group is *anti* to the methyl, as expected, the diethyl amino butyl (antimalarial) side chain will be added to force the formyl and methyl groups into the correct stereochemical position for attack and subsequent ring formation, as illustrated below:

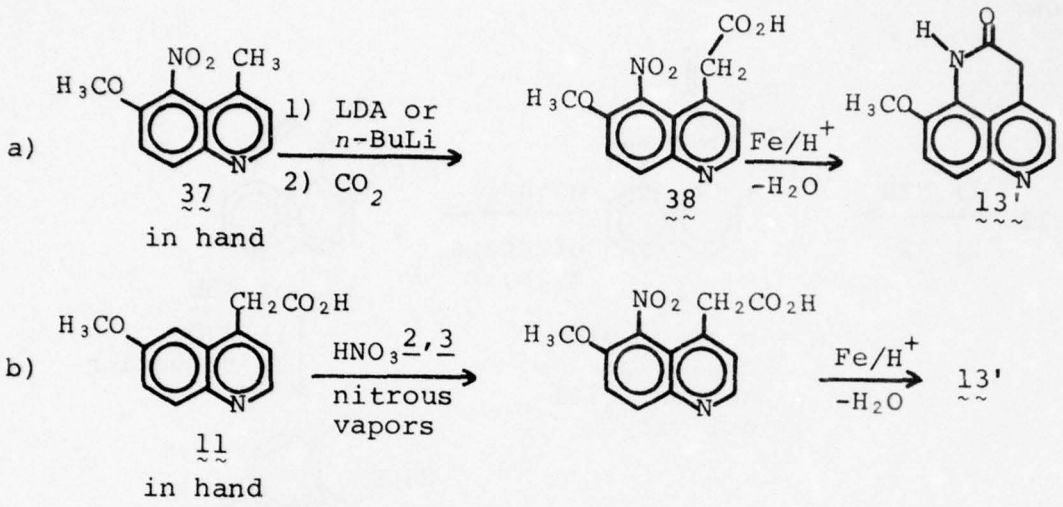



Another possibility similar to the Madelung approach is built around the chemistry of urethanes to generate a better leaving group for the carbanionic carbon to displace and is shown as follows:

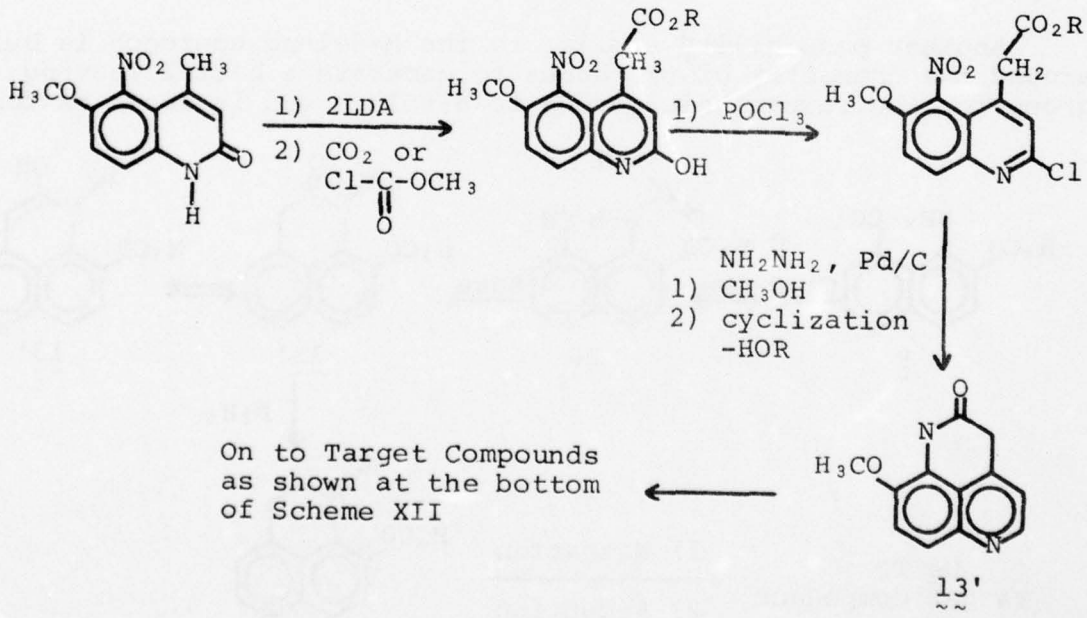


Scheme XIII

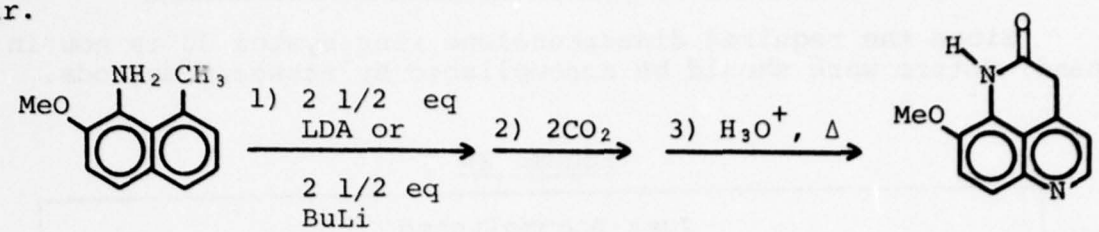
Carbonylation Approach




If nitration in the 5-position of 11 does not work well in the second case (b) one can go by the pathway illustrated below, albeit, it is somewhat longer.



The following pathway to the 9-OMe analogs has been selected as the route of choice. It must be scaled up in the second year.



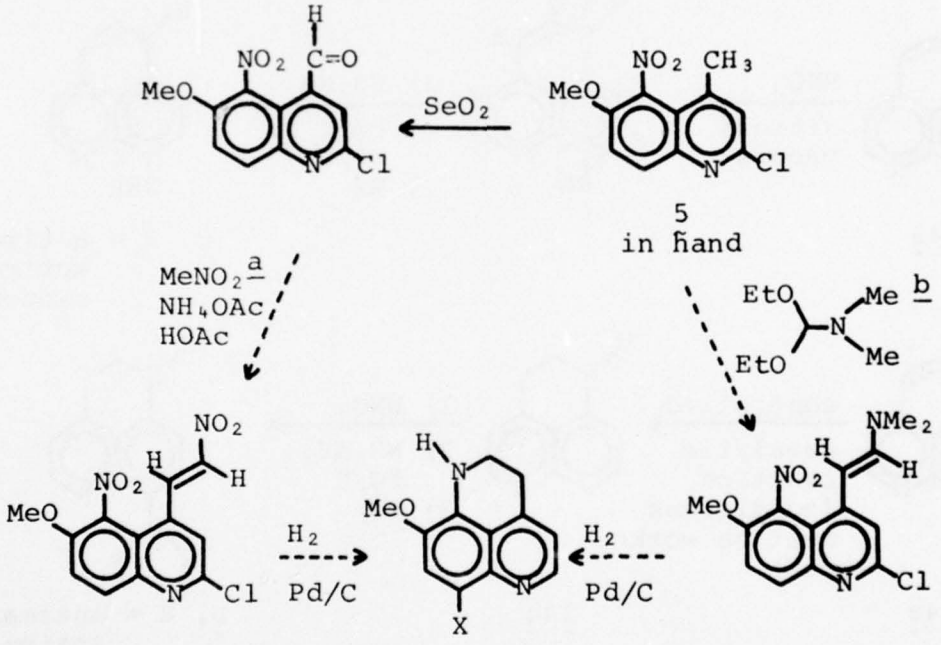

8 13'

*This reaction has just been completed. The mass spectrum shows a molecular ion consistent with 13'; nmr and ir data also support the structure of 13'.

Scheme XIV

4-Carboxaldehyde Approach

The impetus for this possible route stems from combined methodologies developed in the indole area by Woodward[a] and Leimgrüber.[b]




13b, X = H
B, $HNO_3$/Fe, $H^+$
X = $NH_2$

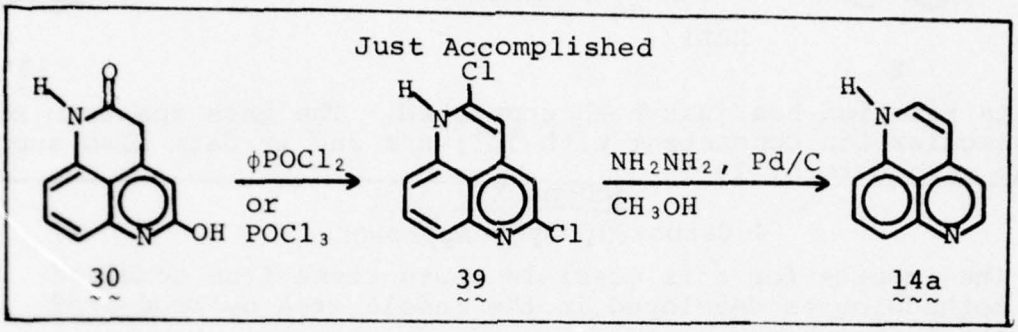
[a]R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, Tetrahedron, 2, 1 (1958).

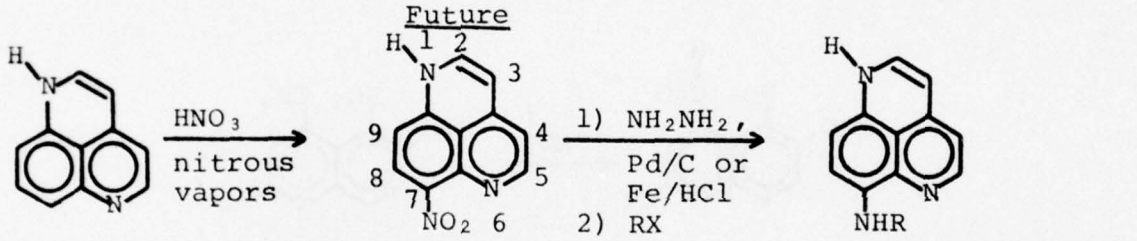
[b]A. D. Batcho and W. Leimgrüber, German Patent 2,057,840; cf. Chem. Abs., 75, P63605v (1971); P. G. Gassman and W. N. Schenk, J. Org. Chem., 42, 3240 (1977).

## Future Proposals in the 9H Diazaphenalene Area

Since the required diazaphenalene ring system 30 is now in hand, future work should be accomplished by standard methods.

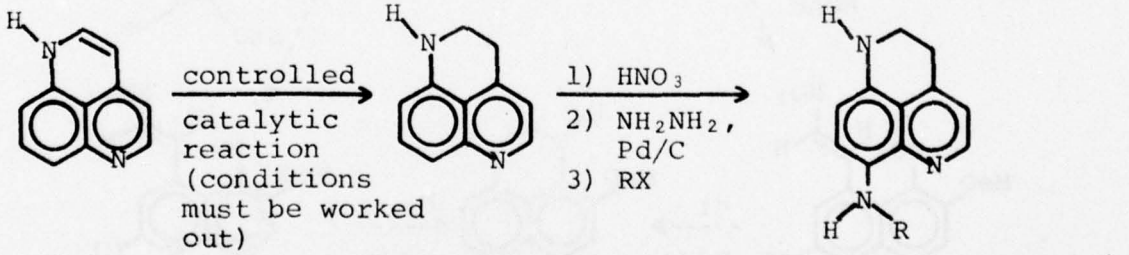
Scheme XV




14a

C, R = antimalarial active sidechain

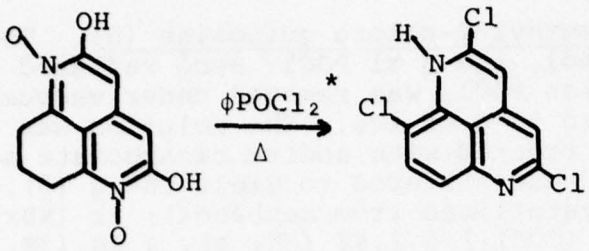



14a 14b

D, R = antimalarial active sidechain

There are at least 10 variations to this approach that could be employed.

*We have just tried the reaction below (August 1): See p. 26




M + 1 (CI, $NH_3$) 271, isotope % shows 3 Cl atoms; NMR ($CF_3CO_2H$) δ 6.67 (s, 1H), 6.70 (s, 1H), 7.35 (d, 1H, $J$ = 8 Hz), 7.97 (d, 1H, $J$ = 8 Hz).

+ one other compound

26

The product has been shown to be the trichloro species drawn directly above.

This excellent and surprising result further simplifies the problem in both the 9H and 9-$OCH_3$ series. Anal. Calcd for $C_{11}H_5N_2Cl_3$: C, 48.62; H, 1.84; N, 10.31. Found: C, 48.96; H, 1.61; N, 10.34.

## Experimental

Microanalyses were performed on an F & M Scientific Corp. Carbon, Hydrogen, Nitrogen Analyzer Model 185. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian T-60 and CFT-20 spectrometers with $Me_4Si$ internal standard. All mass spectra were taken on either a Hitachi Perkin-Elmer RMU-6 or AEI MS 902 instrument. Infrared spectra were obtained on a Beckman IR-8 in either chloroform or KBr. Analytical TLC was performed on EM precoated sheets, silica gel F-254, 0.25 mm thickness while column chromatography was carried out with Baker Analyzed silica gel 60-200 mesh. Some ir spectra were recorded on a Beckman Acculab 1 spectrometer.

Dimedone, cyclohexane-1,3-dione, dimethyl β-ketoglutarate, and N-benzylamine were purchased from Aldrich Chemical Co. The citrate-phosphate buffer (pH 5.5) was prepared by dissolving $Na_2HPO_4 \cdot 7H_2O$ (2.60 g) and citric acid (0.82 g) in water (200 ml).

4-Methyl-6-methoxy-2-quinolone (3) (1). The starting quinolone was prepared from p-anisidine (1) and ethylacetoacetate by the method of Campbell, Elderfield and coworkers (1). All melting points of the derivatives prepared by this sequence of reactions were in complete agreement with the literature values (1).

6-Methoxy-5-nitro-4-methyl-2-hydroxy quinoline (4) (2). A current of nitrous vapors (3) (from $As_2O_3$ and $HNO_3$) was passed (3) through a solution of 2 g (.01 mol) of 6-methoxy-4-methyl-2-hydroxy quinoline (3) in 30 ml glacial acetic acid for 30 min. The solution was then poured into 250 ml $H_2O$ and filtered, yielding 6-methoxy-5-nitro-4-methyl-2-hydroxy quinoline (4), 2.1 g, 90%, mp mp 278-282° (recrystallized from methanol); ir (KBr) 1520 $cm^{-1}$ ($ArNO_2$ asymmetric N-O stretch), 800 $cm^{-1}$ ($ArNO_2$ C-N stretch), $M^+$ at 234.

Anal. Calcd for $C_{11}H_{10}O_4N_2$: C, 56.41; H, 4.27; N, 11.96. Found: C, 56.93; H, 4.00; N, 11.85.

6-Methoxy-5-nitro-4-methyl-2-chloro quinoline (5). The quinolone (4), 1 g, .004 mol, and 5 ml $POCl_3$ were refluxed for 1 hr and cooled (1). Excess $POCl_3$ was removed under vacuum and the residue was poured onto 50 g of ice. The solution was filtered and the solid product was treated with sodium bicarbonate solution until effervescence stopped and filtered to yield .80 g (5), 80% yield: mp 225-230° (recrystallized from methanol); ir (KBr) 1100 $cm^{-1}$ (Ar-Cl stretch); NMR ($CDCl_3$) $\delta$ 2.62 (3H, s), 4.10 (3H, s), 7.38 (1H, s), 7.60 (1H, d), 8.20 (1H, d), mass spectrum at *m/e* 254 (74), 252 ($M^+$, 100), 222 (100), 207 (91), 188 (97), 176 (90), 163 (100), 128 (93), 89 (38).

Anal. Calcd for $C_{11}H_9N_2O_3Cl$: C, 52.27; H, 3.56; N, 11.11. Found: C, 52.00; H, 3.35; N, 11.00.

4-Methyl-5-amino-6-methoxy quinoline (8). To a magnetically stirred mixture of 2-chloro-4-methyl-5-nitro-6-methoxy quinoline (5) (5 g, 20 mmol) and Pd/C (1 g, 5%) in methanol (300 ml) was added 15 ml of 95% hydrazine (4) in methanol (15 ml) dropwise. The mixture was refluxed for 6 hr and an additional 15 ml of hydrazine in 15 ml methanol was added and refluxing was continued overnight. The mixture was then cooled, filtered, and solvent was removed under reduced pressure. Water (100 ml) was added and the residue was extracted with ethyl acetate ( 3 x 125 ml). The combined extracts were dried ($Na_2SO_4$) and column chromatography on silica (eluent, benzene-ethyl acetate) provided 2.7 g (73%) of the amine (8): mp 85-87° (Skelly B); ir (KBr) 3420, 3340 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 8.6 (d, 1H), 7.6 (d, 1H), 7.4 (d, 1H), 7.0,(d, 1H), 4.0 (s, 3H), 3.0 (s, 3H), 4.6 (s, 2H); mass spectrum *m/e* 188 (86, $M^+$) 174 (100), 145 (62), 117 (8), 77 (6). (Note: alumina may also be used for the chromatography-eluting with benzene-ethyl acetate).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.43; N, 14.89. Found: C, 70.12; H, 6.61; N, 15.27.

4-Methyl-5-formamido-6-methoxy quinoline (12). Acetic-formic anhydride (7) was prepared by stirring acetic anhydride (10.2 ml) and formic acid (4.3 ml) for 2 hr at room temp. This solution (0.91 ml, 7 mmol) was then added slowly to a solution of 4-methyl-5-amino-6-methoxy quinoline (8) (1.0 g, 5.3 mmol) in 40 ml benzene. A precipitate began to form and the solution was stirred overnight, and filtered to provide the N-formyl compound (12, 1.1 g, 96%): mp 194-196° (methanol); ir (KBr) 3210, 1650 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.60 (s, 3H), 3.95 (s, 3H), 7.20 (d, 1H, $J$ = 4 Hz), 8.30 (d, 1H, $J$ = 9 Hz), 8.65 (1H, d, $J$ = 4 Hz), 9.10 (1H, s), and 7.60 (d, 1H, $J$ = 9 Hz); $M^+$ at *m/e* 216 (100), 201 (20), 188 (15), 173 (95), 155 (5), 145 (20).

Anal. Calcd for $C_{12}H_{12}O_2N_2$: C, 66.66; H, 5.55; N, 12.96. Found: C, 66.96; H, 5.78; N, 12.91.

Carbonylation of 4-methyl-6-methoxy quinoline (10) to provide the carboxylic acid (11). The combined procedures of Uskokovic (5) [J. Am. Chem. Soc., 100, 576 (1978)] and Wolfe *et al.* (6) [J. Org. Chem., 34, 3263 (1969)] were employed in this reaction. The 6-methoxy quinoline derivative (10, 0.01 eq) was dissolved in dry tetrahydrofuran (50 ml). Lithium diisopropyl amide was prepared and added to the solution at low temperature. After the anion formed, it was quenched by pouring onto dry ice. The yield of carboxylic acid (11) was greater than 80%: ir (KBr) 3400, 3000-2400 (broad band), 1715 (C=O), 1600, 1210, 1245, 1100, and 1000 $cm^{-1}$. The singlet (4-$CH_3$) at 3.00 $\delta$ in the spectrum of the starting material now has disappeared and the carboxyl proton below 9 ($\delta$) does exchange on treatment with $D_2O$, substantiating the structure of the carbonylation product 11.

Attempted carbonylation of 4-methyl-5-amino-6-methoxy quinoline (8) with LDA and $CO_2$. The 5-amino-4-methyl derivative (8, 0.01 mol) was dissolved in THF and 2 eq of LDA were added at low temperature. The mixture was stirred until a colored solution formed which indicated carbanion formation had ensued. The reaction was quenched with $CO_2$ to provide a new yellow, high melting crystalline solid which appears to be homogeneous by tlc. This reaction was only carried out in early August and the structure has not been verified. Ir (KBr) 3300, 3200, 1640, 1620, and 1590 $cm^{-1}$ appear to be the strongest absorptions in this new compound. $M^+$ at *m/e* 314, very recent result, must be repeated.

Attempted cyclization of the formamide (12) to the 9-methoxy diazaphenalene derivative (13). We have only had time to try two reactions in this series, to date. Much work must be done to determine the correct reaction conditions (8). (A) The formamide (12) was heated to reflux in a *t*-butanol, potassium *t*-butoxide solution. The product of this reaction was the amine (8), hydrolysis of the formyl group had occurred. (B) The formamide (12) and *t*-butoxide (solid) were heated to 250° in a Rose's metal bath. The reaction bubbled as it should, however, much decomposition occurred. Chromatography of the products is now in progress. The process that has occurred we hope is a Madelung "type" cyclization (8).

5,6,7,8-Tetrahydro-5-hydroxyimino-2-quinolon-4-ylacetic acid (20). To a suspension of the acid 19 (22.1 g, 0.10 mol) in 95% EtOH (100 ml) was added a solution of hydroxylamine hydrochloride (10.44 g, 0.15 mol) and sodium acetate (12.6 g, .0153 mol) in water (70 ml). The mixture was refluxed for 4 hr and cooled. The precipitate was filtered from solution, washed with water and methanol to provide 20 (22.8 g, 96% yield) as yellow plates: mp 226-230° (turned from a yellow solid to an orange compound); ir (KBr) 3310 (m), 2860 (broad), 1702 (s), 1642 (s), 1598 (sh, s), 955 (m), and 938 $cm^{-1}$ (m); NMR ($D_2O$ + NaOD) $\delta$ 1.82 (m, 2H), 2.61 (m, 4H), 3.80 (s, 2H), and 6.18 (s, 1H); CI mass spectrum ($NH_3$) *m/e* (rel intensity) 237 (M + 1, 1), 220 (6), 219 [(M + 1) - 18, 42], 218 (3), 204 (13), 203 [(M + 1) - 34, 100], 202 (8), 193 (48), 178 (29), 177 (10), 125 (12), 83 (24), 82 (12).

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.08; N, 11.86. Found: C, 55.89; H, 5.12; N, 11.68.

The same oxime (20) was also obtained when 19 and $NH_2OH \cdot HCl$ were heated in a pyridine/ethanol solution for several hours and worked up as mentioned above. The yield was 93-95%.

Hydroxyimine hydroxamic acid (22). A solution of $NH_2OH \cdot HCl$ (1.05 g, 0.015 mol) and AcONa (1.24 g, 0.0151 mol) in $H_2O$ (10 ml) was added to a suspension of ester 18 (2.35 g, 0.01 mol) in 95% EtOH (15 ml) and the mixture was refluxed for 5 hr. The precipitate was filtered from the solution, washed with water and methanol to provide 22 (1.45 g) as yellow plates: mp 228-230° (turned from a yellow solid to the orange compound 21); ir (KBr) 3100-2300 (broad bands), 1640 (s), 1620 (s), 1588 (s), 1516 (s), 1422 (s), 1180 (s), 980 (m), 960 (m) $cm^{-1}$. CI mass spectrum ($NH_3$) *m/e* (rel intensity) 236 (13), 220 (19), 219 [(M + 1) - 33, 100], 218 (5), 204 (10), 203 (73), 202 (3).

Anal. Calcd for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.18; N, 16.73. Found: C, 52.00; H, 5.14; N, 16.24.

7,8-Dihydro-2,5-dihydroxy-1,6-diazaphenalene-1-oxide (21). (A) The oxime (20) (23.6 g, 0.1 mol) was boiled in hydrochloric acid (150 ml, 10%) for 30 minutes. On cooling a yellow-orange substance crystallized from the solution. The material was filtered, washed with water, followed by methanol, and dried to give yellow-orange crystals (21, 21 g, 96% yield): mp > 350°; ir (KBr) 3400 (broad), 3040 (m), 1620 (s), 1595 (s), 1480 (w), 1430 (sh, m), 1360 (sh, w), 1295 (m), 1180 (s), 960 (m), 830 (m), 740 (m), 705 (w); NMR ($CF_3COOH$) $\delta$ 2.38 (m, 2H), 3.4 (m, 4H), 6.95 (s, 1H), 7.0 (s, 1H); NMR ($D_2O$ + NaOH) $\delta$ 2.2 (m, 2H), 2.94 (t, 2H), 3.2 (t, 2H), 6.05 (s, H), 6.2 (2, 1H); CI mass spectrum ($NH_3$) *m/e* (rel intensity) 236 (M + 18, 3), 221 (5), 220 (12), 219 (M + 1) 80), 218 (4), 217 (2), 205 (5), 204 (14), 203 [(M + 1) - 16, 100], 202 (5), 201 (5), 200 (1).

Anal. Calcd for $C_{11}H_{10}N_2O_3$(218): C, 60.55; H, 4.62; N, 12.84. Found: C, 60.36; H, 4.55; N, 12.53.

N.B. The color of this compound is yellow when suspended in acidic or alkaline solution, while orange when it is dried or suspended in water.

(B) Compound 21 was also obtained when compound 22 was treated with 10% HCl in a similar manner and in the same yield.

(C) To a suspension of ester 18 (2.35 g, 0.01 mol) in absolute EtOH (15 ml) were added $NH_2OH \cdot HCl$ (1.05 g, 0.03 mol) and dry pyridine (5 ml). The mixture was refluxed for 6 hr and precipitate was collected by filtration and washed with water. The N-oxide (21) was obtained in 84% yield (1.81 g).

(D) A small amount of oxime 20 was heated to 226° in a capillary tube. A yellow-orange solid of 21 was obtained. The ir spectrum of this solid was identical to that of N-oxide obtained from (A).

7,8-Dihydro-2,5-dihydroxy-1,6-diazaphenalene-1,6-dioxide (26). A solution of $NH_2OH \cdot HCl$ (10.44 g, 0.15 mol) and AcONa (12.67 g, 0.0154 mol) in $H_2O$ (60 ml) was added to a suspension of the coumarin ester 17 (11.8 g, 0.05 mol) in 95% EtOH (60 ml) and the mixture was refluxed for 10 hr. A yellow precipitate was filtered from the solution and washed with water to provide a mixture of 26 and 25. To the mother liquor was added another portion of $NH_2OH \cdot HCl$ (3.48 g, 0.05 mol) and AcONa (4.13 g, 0.05 mol) and the mixture was refluxed for 8 hr. An additional 3.8 g of yellow solid was obtained. The combined precipitate was treated with hot 10% HCl (90 ml) to give pure 26 (10.3 g, 88% yield) as yellow-orange crystals: mp > 300°; ir (KBr) 3450 (broad), 3050 (s), 1630 (s), 1610 (s), 1295 (s), 1190 $cm^{-1}$ (s); NMR ($CF_3COOH$) δ 2.52 (m, 2H, C-8H s), 3.62 (t, 4H, $J$ = 6 Hz, C-7 and C-9H) and 7.00 (s, 2H); mass spectrum (70 ev) *m/e* (rel intensity) 203 (14), 202 ($M^+$ - 32, 100), 201 (20), 200 (61), 177 (23), 174 (39), 149 (46); CI mass spectrum ($NH_3$) *m/e* (rel intensity) 237 (4), 236 (16), 235 (M + 1, 100), 234 (10), 233 (4), 220 (16), 219 [(M + 1) - 16, 92], 218 (17), 217 (10), 204 (9), 203 [(M + 1) - 32, 52], 202 (8), 201 (6).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.27; N, 11.97. Found: C, 56.65; H, 4.27; N, 11.73.

4-Methyl-5,6,7,8-tetrahydro-5-oxo-2-hydroxy quinoline (27) (following a similar procedure by Wolfe *et al.* (6). (A) 5,6,7,8-Tetrahydro-5-oxo-2-quinolon-4-yl acetic acid 19 (4.0 g, 0.017 mol) was heated under $N_2$ until it melted. The product sublimed as a white solid: mp 274-276° (3.2 g, quantitative yield).

In another experiment, the acid (19) was melted under $N_2$ and the product was treated with charcoal in a mixture of chloroform and ethanol to give the desired product 27 again in excellent yield: ir (KBr) 3420 (broad), 2920 (b), 1680 (m), 1650 (s), 1600 (m), 1420 (s), 1290 (m), 1200 (m) $cm^{-1}$; NMR ($CDCl_3$) δ 2.21 (q, 2H), 2.6 (s, 3H), 3.0 (m, 4H), 6.32 (s, 1H); CI mass spectrum ($NH_3$) *m/e* (rel intensity) 179 (4), 178 (M + 1, 100), 177 (2).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.79; H, 6.21; N, 7.91. Found: C, 68.45; H, 6.27; N, 7.96;

(B) The acid 19 (1.18 g, 0.05 mol) was refluxed overnight in a mixture of acetic acid (20 ml) and concentrated HCl (5 ml). The acidic solution was made alkaline with sodium hydroxide (4 *N*) and then extracted with chloroform (3 x 25 ml). The combined extracts were washed with water, then dried ($Na_2SO_4$) and the solvent removed under reduced pressure to yield 27 (0.1 g, 11% yield): mp 274-276°; identical in all respects with the product isolated in the previous experiment.

4-Methyl-5,6,7,8-tetrahydro-5-hydroxyimino-2-hydroxy quinoline (28). (A) Compound 27 (8.0 g, 0.04 mol), hydroxylamine hydrochloride (4.2 g, 0.06 mol) and sodium acetate (4.0 g, 0.06 mol) were refluxed in a mixture of ethanol (40 ml) and water (40 ml) for 3 hr. At the end of the reaction a heavy white precipitate had formed. The reaction mixture was cooled, filtered, and the solid washed with water to provide a white crystalline product. The hydroxyimino derivative crystallized from aqueous alcohol as a white powder 28: mp 308-310° (8.0 g, 93%); ir (KBr) 3200 (broad), 1625 (s), 1600 (w), 1390 (m), 1200 (m) $cm^{-1}$; NMR ($CF_3COOD$) $\delta$ 2.23 (m, 2H), 2.7 (s, 3H), 3.06 (t, 2H), 6.97 (s, 1H), 7.33 (s, 1H). On addition of $D_2O$, the singlet at 6.97 disappeared. CI mass spectrum ($NH_3$) *m/e* (rel intensity) 193 (M + 1, 100).

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.57. Found: C, 62.60; H, 6.52; N, 14.38.

(B) Compound 27 (2g, 0.011 mol), hydroxylamine hydrochloride (2 g, 0.028 mol), potassium hydroxide (6 g, 0.11 mol), alcohol (40 ml), and water (10 ml) were refluxed for 20 hr. The reaction was worked up as mentioned above to provide compound 28, identical in all respects with the product isolated in the previous experiment (2.0 g, 92%).

4-Methyl-5,6,7,8-tetrahydro-5-hydroxyimino-2-hydroxy quinoline acetate (29a). Compound 28 (0.5 g, 0.003 mol) was dissolved in a mixture of acetic acid (4 ml) and acetic anhydride (1.5 ml). The reaction mixture was saturated with HCl gas and then refluxed for 1 hr. The light brown colored solution was left to cool and then diluted with water to give a white crystalline product crystallized from alcohol (29a): mp 268-270° (0.43 g, 70%); ir (KBr) 3450 (broad), 2910 (broad), 1760 (s), 1650 (s), 1610 (w), 1580 (w), 1410 (s), 1200 (s) $cm^{-1}$; NMR (warm DMSO) $\delta$ 1.63 (q, 2H), 2.2 (s, 3H), 2.4 (s, 3H), 2.6 (m, 4H), 6.1 (s, 1H); CI mass spectrum ($NH_3$) *m/e* (rel intensity) 236 (18), 235 (M + 1, 100), 177 (15).

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.54; H, 5.98; N, 11.96. Found: C, 62.29; H, 5.95; N, 12.02.

5-Acetamide-4-methyl-2-hydroxy quinoline (29). Compound 28 (0.5 g, 0.003 mol) was dissolved in a mixture of acetic acid (4 ml) and acetic anhydride (1.5 ml). The reaction mixture was saturated with HCl gas and refluxed for 18 hr. At the end of the reaction, the color of the solution became dark and it was cooled, diluted with water and left to stand. A white precipitate formed, it was filtered off and washed with water to give a white crystalline compound of 29, crude mp 345-348°, which crystallized from alcohol, mp 355° (295 mg, 53%): ir (KBr) 3280 (m), 1690 (s), 1650 (s), 1610 (w), 1535 (m), 1430 (m), 1380 (m), 1270 (m); NMR (warm DMSO 220 M Hz) $\delta$ 2.04 (s, 3H), 2.41 (d, 3H, $J$ = 5 Hz), 6.32 (s, 1H), 6.93 (d, 1H), 7.25 (d, 1H), 7.43 (t, 1H), 9.72 (s, 1H); CI mass spectrum ($NH_3$) *m/e* (rel intensity) 234 (4), 218 (16), 217 (M + 1, 100), 216 (14), 215 (14).

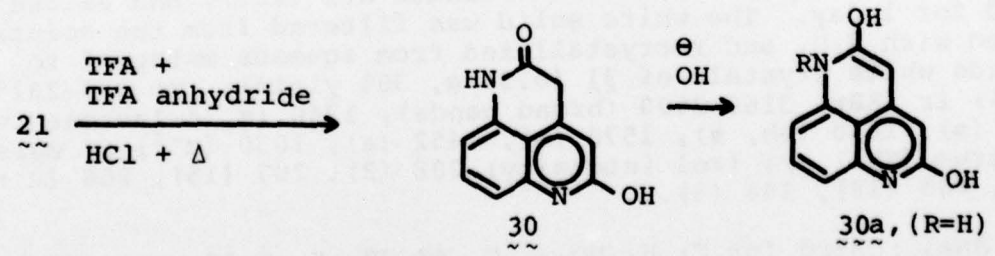
Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.50; N, 12.96. Found: C, 66.41; H, 5.28; N, 13.05.

2,5-Dihydroxy-1,6-diazaphenalene-1-acetamide (30a). Compound 21 (2.0 g, 0.009 mol) was dissolved in acetic acid (32 ml) and acetic anhydride (12 ml); the solution was saturated with HCl gas. The reaction mixture was refluxed for 18 hr, cooled, diluted with water and the precipitate formed upon standing was filtered off and washed with water to give an olive green solid of 30a. It crystallized from acetic acid as olive green crystals (30a): mp > 350° (1.7 g, 86% yield); ir (KBr) 3200 (broad), 1670 (s), 1630 (m), 1600 (m), 1370 (w), 1300 (m) $cm^{-1}$; NMR (warm DMSO 220 MHz) δ 2.51 (s), 6.21 (s), 6.63 (d), 6.81 (t), 7.34 (t), 10.59 (s); NMR (warm DMSO) δ 2.50 (s, 3H), 6.2 (s, H), 6.6-7.3 (m, 4H), 10.57 (s, 1H), 11.6 (s, 1H). By the addition of $D_2O$, the 2 singlets downfield disappeared. NMR ($CF_3COOH$) δ 2.8 (s, 3H), 7.0-8.0 (imposing m, 5H); CI mass spectrum ($NH_3$) *m/e* (rel intensity) 244 (19), 243 (M + 1, 100), 242 (17), 201 (13).

Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.13; N, 11.57. Found: C, 64.43; H, 3.97; N, 11.48.

N.B. When the reaction was scaled up to 8 g, the yield was lower and some combined material contaminated 30a, R=$\overset{O}{\overset{\|}{C}}-CH_3$).

When the reaction was scaled up to above the 10 g level, the yield of 30a was lower and the product was contaminated with tarry material which was difficult to remove. A very promising alternative route was developed by using a mixture of trifluoroacetic acid and trifluoroacetic anhydride as a solvent for this reaction. This technique provided the diazaphenalene 30 (R = H) directly in almost quantitative yield which appeared to be in the keto form (30). Compound 30c exhibited an off-white color and its structure was confirmed by ir, NMR, mass spectra. Moreover, upon treatment of 30 with hot alkali it gave the brick red compound felt to be the hydroxypyridine form 30a, R=H.




5-Hydroxy-2-oxo-2,3-dihydro-1,6-diazaphenalene 30, (R=H)-the keto form. Compound 21 (8.0 g, 0.037 mol) was dissolved in trifluoroacetic acid (30 ml). The reaction mixture was saturated with HCl gas and cooled to room temp. Trifluoroacetic anhydride (15 ml) was added and the reaction mixture was refluxed for 18 hr. The reaction mixture was cooled and diluted with water whereupon

a heavy precipitate formed. It was filtered off and washed with water to give a pale yellow solid which was crystallized from a mixture of trifluoroacetic acid and alcohol, to give an off-white powder (30): mp= 390° (7.0 g, 96% yield); ir (KBr) 1690 (sh, m), 1650 (s), 1620 (s), 1560 (m), 1450 (m), 1350 (m), 1190 (m) $cm^{-1}$; NMR ($CF_3COOH$) δ 3.9 (s, 2H), between 7.17 and 8.06 (several signals 5H); CI mass spectrum ($NH_3$) *m/e* (rel intensity) 218 (9), 202 (13), 201 (M + 1, 100), 200 (5).

Anal. Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.78; H, 3.76; N, 14.31.

2,5-Dihydroxy-1,6-diazaphenalene (30a) (A) Compound 30a (R=C-$CH_3$, 0.08g)was refluxed in aqueous sodium hydroxide (10 ml, 4 *N*) for 3 hr. The reaction mixture was cooled and diluted with water, filtered to give brick red solid, crystallized from a mixture of trifluoroacetic acid and alcohol as a brick red powder (30): mp > 400° (0.48 g, 60% yield); ir (KBr) 3200 (m), 1670 (s), 1630 (s), 1600 (s), 1520 (m), 1310 (m) $cm^{-1}$; NMR ($CF_3COOH$) showed only multiplets between δ 7.78 and 8.50; CI mass spectrum ($NH_3$) *m/e* (rel intensity) 218 (4), 202 (21), 201 (M + 1, 100), 200 (7).

Anal. Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.79; H, 2.50; N, 13.51. H is low.

(B) Compound 30 (250 mg, 0.001 mol) was refluxed in aqueous sodium hydroxide (10 ml, 4 *N*) for 5 hr. The reaction mixture was cooled, diluted with water and then neutralized with acetic acid. The precipitate formed was filtered off and washed with water to give brick red solid which crystallized from acetic acid (30a): mp > 400° (170 mg, 82%) identical in all respects with the product obtained in the last experiment.

Lactone 31 of 5,6,7,8-tetrahydro-5-oxo-2-quinolon-4-ylacetic acid. To a solution of keto acid 19 (1.23 g, 0.0056 mol) in 0.2 *N* aqueous sodium hydroxide (15 ml) was added 0.4 g of $NaBH_4$. After the solution had been stirred at room temperature for 45 hr, it was cooled to 0°, acidified with dilute HCl (10%), and allowed to stand for 1 day. The white solid was filtered from the solution, washed with $H_2O$, and recrystallized from aqueous methanol to provide white crystals of 31 (0.35 g, 30% yield): mp 229-232° (dec); ir (KBr) 3160-2600 (broad bands), 1760 (s, δ-lactone C=O), 1659 (s), 1640 (sh, s), 1570 (m), 1452 (s), 1030 ($m^{-1}$; CI mass spectrum (NH ) *m/e* (rel intensity) 208 (2), 207 (15), 206 (M + 1, 100), 205 (18), 204 (3).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.39; H, 5.37; N, 6.83. Found: C, 64.32; H, 5.37; N, 6.93.

Concentration of the remaining mother liquors followed by filtration afforded 5,6,7,8-tetrahydro-5-hydroxy-2-quinolon-4-acetic acid (32) (0.41 g) as white plates.

Methyl-7,8-dihydro-2-quinolon-4-yl acetate (33). The lactone

31 (0.2 g, 0.00097 mol) was dissolved in methanolic HCl and the solution refluxed for 24 hr. The methanol was removed under reduced pressure and the residue was taken up in chloroform. The organic layer was washed with aqueous potassium carbonate (10 ml) and water (10 ml) and then dried ($MgSO_4$). The methyl ester 33 (0.091 g, 43% yield) was obtained by column chromatography over silica gel as a white powder: mp 179-180°; ir (KBr) 3020-2760 (broad), 1732 (s), 1660 (s), 1635 (sh, m), 1345 (m) $cm^{-1}$; NMR ($CDCl_3$) δ 2.34 (m, 2H), 2.89 (t, 2H), 3.53 (s, 2H), 2.72 (s, 3H), 5.82 (m, 1H), 6.30 (d, 1H), 6.34 (s, 1H); mass spectrum (80 eV) *m/e* (rel intensity) 219 ($M^+$, 100), 217 (12), 186 (2), 160 (3).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.94; N, 6.39. Found: C, 66.12; H, 6.20; N, 6.36.

5,6,7,8-Tetrahydro-5-hydroxy-2-quinolon-4-yl acetamide (34). A suspension of lactone 31 (1.4 g, 0.0068 mol) in dry ethanol (180 ml) saturated with ammonia gas was heated for 1 hr at 100° on a water bath. The precipitate was filtered from the solution and washed with MeOH to give 34 as a white powder (0.964 g, 64% yield): mp > 300°; ir (KBr) 3250-2700 (broad), 1650 (s), 1610 (s), 1580 (s), 1550 (s), 1450 (s), 1350 (s) $cm^{-1}$; CI mass spectrum ($NH_3$) *m/e* (rel intensity) 206 [(M + 1) - 17, 45], 205 (38), 163 (19), 162 (100), 161 (29), 160 (23).

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.46; H, 6.31; N, 12.61. Found: C, 59.28; H, 6.41; N, 12.28.

Attempted chlorination of methyl ester 18 with $POCl_3$. The ester 18 (1.15 g) was heated with $POCl_3$ (10 ml) at 100-120° for 3 hr. The excess $POCl_3$ was distilled under reduced pressure and the residue was poured onto ice. The cold solution was basified with concentrated ammonium hydroxide and precipitate was filtered from solution. A small amount of the 2-chloro compound (0.122 g) was obtained by column chromatography over silica gel: mp 98-99°; mass spectrum (80 eV) *m/e* 253 ($M^+$, 100). No further attempts to maximize this yield have been made.

Attempted reductive amination of the acid 19. The acid 19 (1.3 g, 0.005 mol), ammonium acetate (7.7 g, 0.1 mol), and sodium cyanoborohydride (434 mg) were dissolved in 50 ml of abs MeOH and the mixture was stirred at room temperature for 48 hr. At the end of the reaction, there was some precipitate. The mixture was cooled and filtered to give ~0.5 g of white crystalline product, mp 330° (color change ~160-165°). Ir and NMR spectra indicated that it is the ammonium salt of the acid. Crystallization from 10% aqueous HCl gave the starting acid. Attempted workup of the filtrate gave mostly inorganic material with no indication of the formation of the amino compound.

Attempted reductive amination of the ester 18. The ester 18 (1.4 g, 0.005 mol), ammonium acetate (3.85 g, 0.05 mol), and $NaCNBH_3$ (200 mg, 0.0035 mol) were stirred in 40 ml abs methanol with molecular sieves ( activated in the oven at 160° for ~2 hr).

The initial pH was ~6. After 2 hr the solution became turbid, 5 ml of glacial AcOH were added (pH ~7). At the end of the reaction (2 days), the solvents were removed on a rotary evaporator at room temperature and the residue extracted with $CHCl_3$. Upon evaporation of the $CHCl_3$, an oily material solidified (possibly due to contamination with AcOH impurity). Recrystallization of this product from MeOH gave a solid which proved to be the starting material (0.8 g) (NMR, ir, tlc evidence).

Attempted reductive amination of the ester 18 in acetic acid. The ester (0.7 g), ammonium acetate (2 g), and $NaCNBH_3$ (120 mg) were dissolved in 20 ml AcOH. The mixture was stirred for 6 days and followed by tlc. On the second day another 120 mg of $NaCNBH_3$ was added. On the third day another 120 mg and 20 ml AcOH was added. There was no indication by tlc of occurrence of any reaction. At the end of the reaction, a small precipitate formed and was filtered from the reaction (mp 265-267°). Again it proved to be the starting acid (0.1 g, ~10% yield). The filtrate was neutralized by ammonium hydroxide, warmed, and left to stand overnight (the color changed to light yellow). The solution was extracted with $CHCl_3$, evaporated to give 0.4 g of the starting ester, mp 220°.

Attempted reduction of oxime 22 with zinc and acetic acid. A suspension of oxime 22 (0.23 g) and zinc dust (2 g) in acetic acid (10 ml) was heated under reflux for 20 hr. After filtrating the white paste from the solution, the solution was made alkaline with dilute NaOH, and extracted with EtOAc, $CHCl_3$. No organic compounds could be obtained from solution.

Methyl-5,6,7,8-tetrahydro-5-oxocoumarin-4-yl acetate (17). Cyclohexane-1,3-dione (15, 22.4 g, 0.20 mol) was dissolved in citrate-phosphate buffer (400 ml), pH 5.5) and stirred for 10 min. To this solution dimethyl β-ketoglutarate (16, 104.4 g, 0.60 mol) was added and after 20 min the cloudy solution became clear. The reaction mixture was stirred at room temperature for 60 days. After 20 days the mixture was seeded with 17 and crystals precipitated from the solution. The white solid was filtered off and the filtrate allowed to stir for the remaining 40 days. Crystals were again filtered from the reaction at the end of the 60-day period. The combined precipitates were recrystallized from methanol to furnish 17 (26.0 g) in 55% yield. An additional 7 g of 17 could be obtained by extraction of the filtrate with chloroform, concentration to small volume, and column chromatography of the residue on silica gel: overall yield 33.0 g, 70% yield; mp 123-125°; uv $\lambda_{max}$ (MeOH) 260 nm (log ε 4.06), 295 (3.74); ir ($CHCl_3$) 1739 (s), 1683 (s), and 1628 (w) $cm^{-1}$; NMR ($CCl_3$) δ 2.16 (m, 2H, $J$ = 6 Hz), 2.53 (t, 2H, $J$ = 6 Hz), 2.90 (t, 2H, $J$ = 6 Hz), 3.72 (s, 3H, OMe), 3.80 (s, 2H), and 6.03 (s, 1H); mass spectrum (80 eV) $m/e$ 236 ($M^+$, 12), 208 (6), 205 (22), 204 (46), 177 (22), 176 (100), 152 (10), 149 (18), 148 (14), 120 (6).

Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02, H, 5.12. Found: C, 61.28; H, 5.28.

4-Methyl-5,6,7,8-tetrahydro-5-oxocoumarin (27). Cyclohexane-1,3-dione (15, 20.0 g, 0.18 mol) and 16 (93.4 g, 0.53 mol) were dissolved in citrate-phosphate buffer (400 ml, pH 5.5) and the mixture was stirred at room temperature for 64 hr. The reaction mixture was then heated for 21 hr, after which time it was cooled and extracted with chloroform (3 x 300 ml) followed by reextraction of the aqueous layer with benzene (3 x 300 ml). The combined organic layers were dried ($Na_2SO_4$) and the solvent removed under reduced pressure. The oily residue was chromatographed on silica gel (Skelly B, benzene, ethyl acetate, gradient elution) to provide 17 (10.6 g, 25%) and 27 (6.4 g, 20%). The oil (27) was dissolved in water from which white crystals precipitated: mp 98-99.5° (lit 98°); uv $\lambda_{max}$ (MeOH) 261 nm (log $\varepsilon$ 3.99), 299 (3.63); ir ($CHCl_3$) 1739 and 1680 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.12 (m, 2H, $J$ = 6 Hz), 2.45 (s, superimposed on a triplet, 5H), 2.85 (t, 2H, $J$ = 6 Hz), and 5.96 (s, 1H); mass spectrum (80 eV) $m/e$ 178 ($M^+$, 43), 150 (72), 122 (100).

Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.67 Found: C, 67.42; H, 5.97.

Conversion of 17 to 27 by acid hydrolysis. Methyl 5,6,7,8-tetrahydro-5-oxocoumarin-4-yl acetate (17, 5.0 g, 0.021 mol) was dissolved in a solution of hydrochloric acid (12 *N*, 40 ml) and glacial acetic acid (50 ml) and the solution was refluxed for 24 hr. The acidic solution was made basic (pH 8) with sodium hydroxide (3 *N*) and then extracted with chloroform (3 x 100 ml). The combined extracts were dried (Na SO ) and the solvent removed under reduced pressure to yield 27 (1.5 g, mp 98°, 41% yield), identical in all respects with 27 isolated in the previous experiment.

Preparation of ethyl 1,2,3,4,5,6,7,8-octahydro-9-methyl-1,8-dioxoxanthen-9-yl acetate and 27 from ethyl acetoacetate and cyclohexane-1,3-dione at pH 5.5. Cyclohexane-1,3-dione (60 g, 0.54 mol) was dissolved in citrate-phosphate buffer (1200 ml, pH 5.5). To the resulting cloudy solution, ethylacetoacetate (200g, 1.54 mol) was added over a 2-min period. The turbid solution became clear and the mixture was allowed to stir at room temperature for 45 days. Tlc indicated the presence of 27 after 1 day. A small portion (200 ml) of the reaction mixture was taken out after 3 days and extracted with chloroform to furnish, after chromatography, a small amount of 27, mp 98°. The remainder of the mixture was allowed to stir until the 45-day period had ended. Crystals of the xanthene (Scheme XI) which formed in the reaction after 30 days, were filtered from the solution and were recrystallized from methanol: mp 140°; uv $\lambda_{max}$ (MeOH) 304 nm (log $\varepsilon$ 3.67), 229 (4.17); ir (KBr) 1730 (s), 1668 (s), 1610 (m), and 1125 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.13 (t, 3H, $J$ = 7 Hz), 1.63 (s, 3H), 1.98 (m, 4H, $J$ = 6 Hz), 2.37 (q, 8H, $J$ = 6 Hz), 3.33 (s, 2H), and 3.97 (q, 2H, $J$ = 7 Hz); mass spectrum (80 eV) $m/e$ 318 ($M^+$, 1). The yield was 50% and no attempt has been made to maximize it.

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.96. Found: C, 67.95; H, 7.18.

5,6,7,8-Tetrahydro-5-oxo-2-quinolon-4-yl acetic acid (18'). Diethyl ether (100 ml), methanol (50 ml), and the 5-oxocoumarin derivative 17 (11.31 g, 0.048 mol) were placed in a round-bottom flask (250 ml) equipped with magnetic stirrer, condenser, and gas inlet tube. Ammonia gas was bubbled into the solution for 15 min until a chalky white precipitate formed, at which time tlc indicated that starting material was no longer present. The white solid was filtered from the solution, washed with aqueous HCl (10%) to provide white needles of 18' (9.55 g, 90% yield): mp 222° dec; uv $\lambda_{max}$ (MeOH) 280 nm (log $\varepsilon$ 4.18) and 317 (sh); ir (KBr) 2985 (s), 1718 (s), 1639 (s), 1586 (sh, m) $cm^{-1}$; mass spectrum (80 eV) *m/e* (rel intensity) 221 ($M^+$, 3), 205 (8), 203 (3), 177 (48), 176 (5), 175 (8), 150 (10), 149 (100), 121 (10), 94 (9), 93 (16), 44 (35).

Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.70; H, 5.07; N, 6.50.

Methyl-5,6,7,8-tetrahydro-5-oxo-quinolon-4-yl acetate (18). The acid 18' (5.23 g, 0.024 m l) was dissolved in methanolic HCl and the solution refluxed for 20 hr. The methanol was removed under reduced pressure and the residue was taken up in methylene chloride. The organic layer was washed with aqueous potassium carbonate (3 x 50 ml) and water (50 ml) and then dried ($MgSO_4$). The methyl ester (18) crystallized from the solution was a white powder (2.92 g, 52% yield), mp 223-224°. An additional 2.2 g of 18 could be obtained by column chromatography over silica gel: overall yield 92%; uv $\lambda_{max}$ (MeOH) 281 nm (log $\varepsilon$ 4.28), 303 (sh), and 317 (sh); ir (KBr) 3400 (broad), 1733 (s), 1632 (s), 984 (m), and 712 (m) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.13 (m, 2.5H, $J$ = 6 Hz), 2.52 (t, 2H, $J$ = 6 Hz), 2.95 (t, 2H, $J$ = 6 Hz), 3.71 (s, 3H), 3.85 (s, 2H), 6.20 (s, 1H), and 13.16 (0.5H) (addition of $D_2O$ reduced the integration of the signal at $\delta$ 2.13 to two protons and eliminated the signal at 13.16); mass spectrum (80 eV) *m/e* (rel intensity) 235 ($M^+$, 21), 204 (20), 203 (40), 176 (30), 175 (100), 149 (7), 147 (7), 120 (8), 119 (10).

Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.50; H, 5.31; N, 5.91.

The last six experiments were taken from a paper [J. Oehldrich and J. M. Cook, J. Org. Chem., 42, 889 (1977)] which was in press when we applied for the contract with the Department of the Army. They are listed here because we have scaled them up to the 100-200 gram levels during the contract period (work done by Mr. Chang and Mr. Mitschka).

2,5-Dichloro-1,6-diazaphenalene (39)

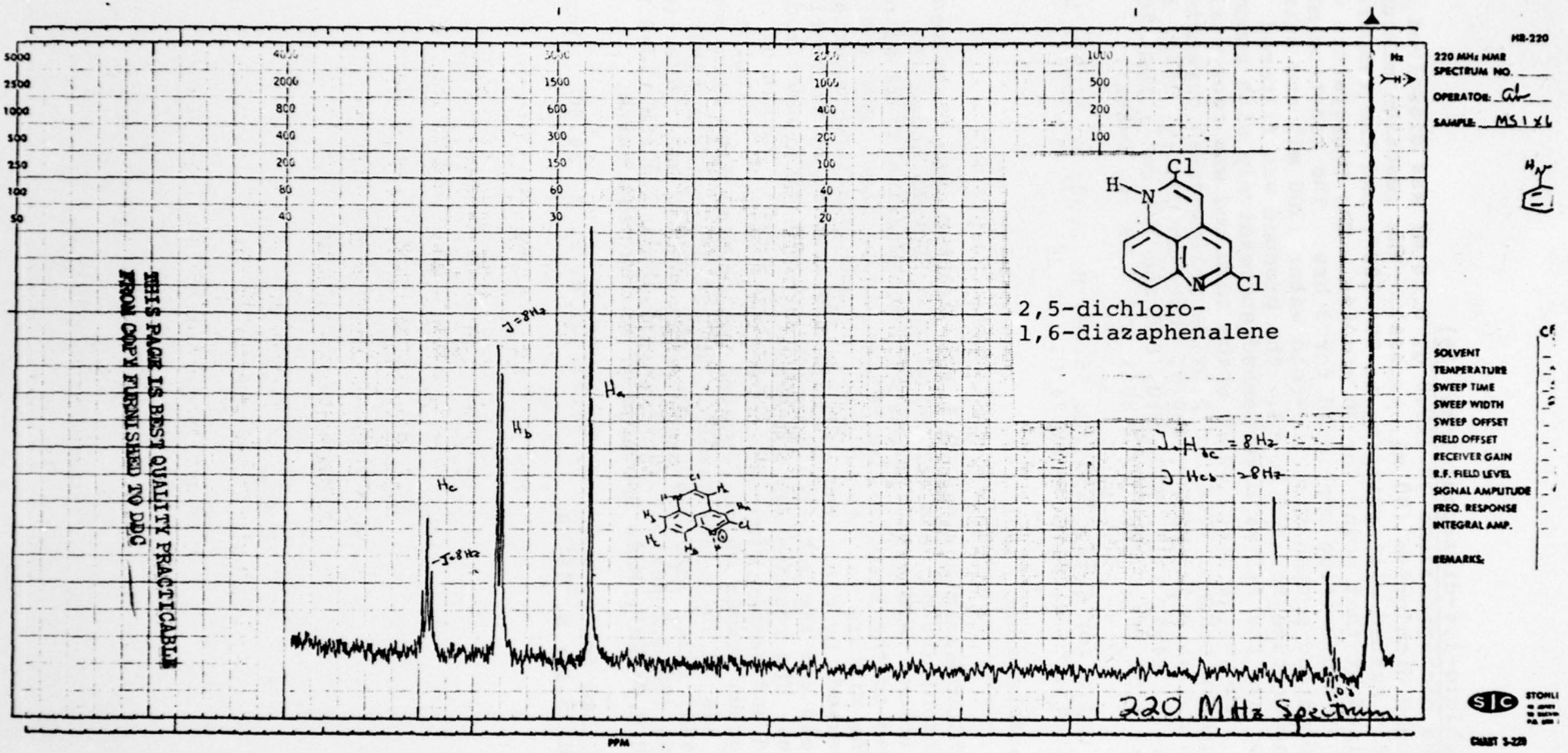
The diazaphenalone 30 (16.0 g, 0.08 m) was dissolved in phenyl phosphonic dichloride (80 ml, excess). The reaction mixture was gradually heated with stirring to 90°-100°; and the temperature maintained at that point for 30 minutes. The temperature was raised to 120-5° and heating continued for 3 hrs. The reaction mixture was cooled and poured into ice-cold water (300 ml) and stirred at room temperature for two hours. The product was filtered from the solution and the filter cake washed successively with ammonia and then water. The yellow-green solid which resulted was recrystallized from aqueous ethanol (70%) to provide yellow-green crystals, mp=223-25° (15 g, 79%); ir (KBr) 3400(w, sharp in $CHCl_3$), 1640, 1605, 1590, 1540, 1470, 1455, 1415, 930, 910, 820 and 770 $cm^{-1}$; NMR δ($CF_3COOH$, 220 mHz) 6.52 (s), 7.28 (d, J=8Hz) and 7.88 (t, J=8Hz).

Anal: Calcd for $C_{11}H_6Cl_2N_2$; C, 55.69; H, 2.53; N, 11.81; Cl, 29.96. Found C, 55.96; H, 2.78; N, 11.74; Cl, 30.26.

1,6-Diazaphenalene (14a)

The dichlorodiazaphenalene 39 (1.2 g, 0.005 m) was dissolved in absolute ethanol (60 ml) and Palladium on carbon was added (5%, 0.4 g) to the solution. Hydrazine (12 ml of 95% hydrazine in 12 ml of ethanol) was added to the reaction, at reflux, in portions over a 4 hour interval. The mixture was heated until no more starting material could be observed by tlc. The catalyst was removed by filtration through filter aid and the mother liquor was concentrated under reduced pressure. The residue was suspended in a small amount of cold water, filtered and washed with aqueous sodium carbonate solution. The yellow green powder which resulted was crystallized from benzene to provide 14a (0.75 g, 88% yield): mp 220-2°; ir(KBr) 3280, 3200, 2650, 1640, 1620, 1580, 1470, 815, 785 and 740 $cm^{-1}$; NMR δ($CD_3OD$, 220 mHz) 5.95 (2H,d,J=6Hz), 6.70 (2H,d,J=8.5Hz), 7.30(1H,t,J=8.5Hz) and 7.42 (2H,d,J=6Hz); Mass Spectrum $M^+$ at 168 mass units.

Anal: Calcd for $C_{11}H_8N_2$; C, 78.55, H, 4.79, N. 16.66. Found C; 77.87; H, 5.12; N, 16.59.






Solvent $CF_3COOH$

mp or bp 218–220 (dec)

ir bands (KBr) 3370 (s), 1625, 1605, 1360, 1124, 830, 780 $cm^{-1}$

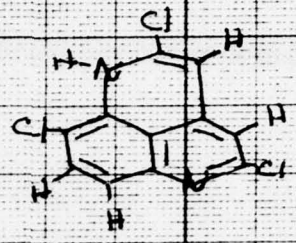
mass spectrum $M^+$ at m/e 270

Base Peak 270

Isotope 2 indicates 3 Cl atoms

Recrystallization Solvent $EtOH-H_2O$

Result August 4
Report at Xerox





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GRAPHIC CONTROLS CORPORATION
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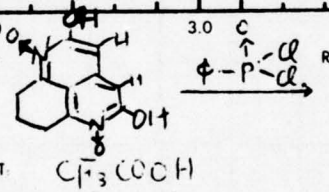

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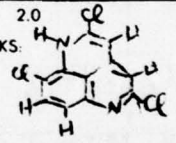

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Original
DATE 7/16/78
repeated August 1, 1978

OPERATOR: CHANG

60 MHz NMR
SPECTRUM NO.

CHN values in annual report

mp ~~bp~~ 225-8°C (dec.)

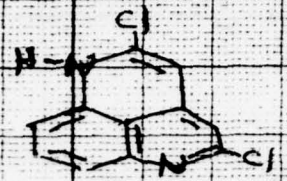
ir bands 3400, 1630, 1600, 1560, 1370, 1230, 900, 820, 760 $cm^{-1}$

mass spectrum $M^+$ at m/e 237 (M+1, 100), (M+1)+2, 64], [(M+1)+4, 10]

Base Peak 237 (100)

Isotope 6 = 2Cl atoms

Recrystallization Solvent alcohol



Result August Report at Xerox

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220 MHz indicates a triplet

impurity

8.0 7.0 6.0 5.0 PPM (δ) 4.0 3.0 2.0 1.0 0

SWEEP OFFSET (Hz): 0

SPECTRUM AMPLITUDE: 320

INTEGRAL AMPLITUDE: 5

SPINNING RATE (RPS): 51

RECORDING CHARTS

GRAPHIC CONTROLS CORPORATION BUFFALO, NEW YORK PRINTED IN U.S.A.

No. VN 1009 (S-60T)

MANUAL

SWEEP TIME (SEC): 50 250

SWEEP WIDTH (Hz): 25 50 100 250 500

FILTER: 1 2 3 4 5 6 7 8

RF POWER LEVEL: 0.04

AUTO ☐ (250) (500) ( 2) (.05)

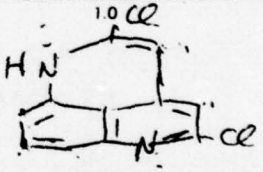
SAMPLE: MS1X67

SOLVENT: TFA/TMS

DATE: 8-9-78

OPERATOR: Mustafa El-Sheikh

REMARKS:



60 MHz NMR SPECTRUM NO.

41

References


1. K. N. Campbell, R. S. Tipson, R. C. Elderfield, B. K. Campbell, M. A. Clapp, W. J. Gensler, D. Morrison, and W. J. Moran, J. Org. Chem., 11, 803 (1946).

2. J. L. C. Marais and O. G. Backeberg, J. Chem. Soc., 2207 (1950).

3. L. Monti and G. F. DiCaporciano, Gazz. Chim. Ital., 69, 745 (1939); the generator employed was similar to that described by A. W. Dox, Org. Syn. Coll. Vol. I, 266 (1932).

4. W. L. Mosby, Chem. Ind., 1348 (1959); W. Parham, R. Davenport, and J. B. Biasotti, Tetrahedron Lett., 557 (1969).

5. J. Gutzwiller and M. R. Uskokovic, J. Am. Chem. Soc., 100, 576 (1978).

6. J. F. Wolfe, G. B. Trimitsis, and D. R. Morris, J. Org. Chem., 34, 3263 (1969); M. J. Weiss and C. R. Hansen, J. Am. Chem. Soc., 71, 2023 (1949)-use of $KNH_2$ as the base.

7. L. Krimen, Org. Syn., 50, 1 (19 ).

8. J. A. Eenkhoorn, Ph.D. Thesis, University of Waterloo, 1971; R. L. Augustine, A. J. Gustausen, S. F. Wanat, I. C. Pattison, K. S. Houghton, and G. Koletar, J. Org. Chem., 38, 3004 (1973).

9. J. Oehldrich and J. M. Cook, J. Org. Chem., 42, 889 (1977).

10. M. Guthzeit, Chem. Ber., 26, 2795 (1893); L. Smith and R. Kelly, J. Am. Chem. Soc., 74, 2300 (1952).

11. Y. Tamura, Y. Kita, and J. Uraoka, Chem. Pharm. Bull., 20, 876 (1972).

12. M. Weigele and W. Leimgruber, Tetrahedron Lett., 715 (1967).

13. (a) H. Shindo, Chem. Pharm. Bull., 8, 845 (1960); (b) G. R. Delpierre and M. Lamchen, Quart. Rev., 329 (1965); (c) E. Moriconi, F. Creegan, C. K. Donovan, and F. A. Spano, J. Org. Chem., 28, 2215 (1963).

14. This phenomenon is under investigation in our laboratory.

15. J. Gottlieb, Ber., 32, 966 (1899); Beilstein, 27, 210 (1937), carbon analysis reported to be low.

16. Y. Tamura, O. Nishikawa, T. Shimizu, M. Akita, and Y. Kita, Chem. Ind., 922 (1975); G. Schroeter, Chem. Ber., 63, 1308 (1930).

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