AD-A134 269 SYNTHESIS OF ANTIMALARIAL AGENTS FROM 23-DIHYDRO-16-DIAZAPHENALENE DERIVATIVES(U) WISCONSIN UNIV-MILWAUKEE DEPT OF CHEMISTRY J M COOK APR 82 1/1

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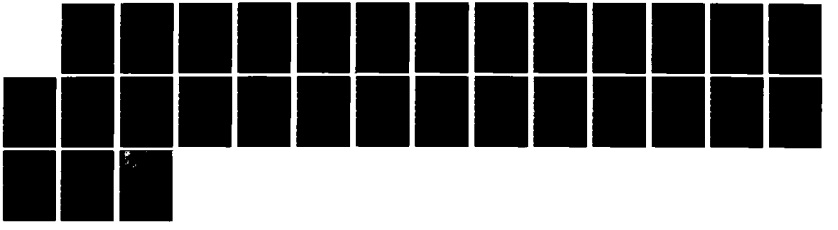

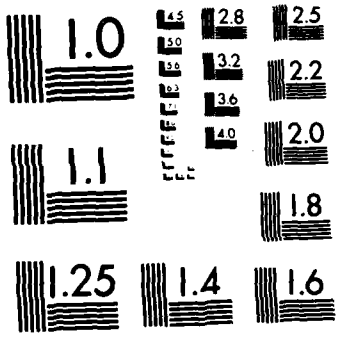

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SYNTHESIS OF ANTIMALARIAL AGENTS FROM 2,3-DIHYDRO-1,6-DIAZAPHENALENE DERIVATIVES

Final Report

October, 1977 to December 31, 1980

JAMES M. COOK

April, 1982

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

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4. TITLE (and Subtitle) Synthesis of Antimalarial Agents from 2,3-Dihydro-1,6-diazaphenalene Derivatives	5. TYPE OF REPORT & PERIOD COVERED Final Report Oct., 1977/Dec. 31, 1980
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19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

1,6-diazaphenalene, 3,8-diaminoquinoline analogs, 9-methoxy-1,6-diazaphenalene, 7-nitro-2,5-dioxo-1,6-diazaphenalene, malaria, leishmaniases

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

The six step synthesis of the new "imidazole-like" heterocycle ,1,6-diazaphenalene (8) from readily available cyclohexane-1,3-dione 1 and dimethyl β-ketoglutarate 2 is described. In addition, a six step synthesis of 9-methoxy-diazaphenalene (34) from ethylacetoacetate and p-ansidine has also been accomplished. An investigation of the chemistry of 9 has been carried out and resulted in several routes to key 7-substituted-1,6-diazaphenalenes (continued)

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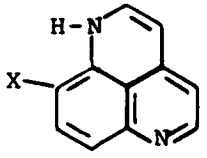
Block #20 - Abstract (continued)

such as 10, 15, 16 and 17, as well as conditions under which to N-alkylate 8. In fact, this alkylation sequence has resulted in



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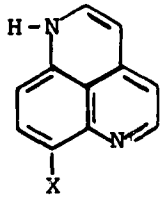

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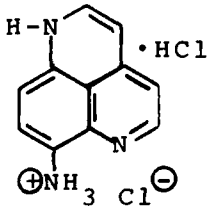
16, X = Br
17, X = I



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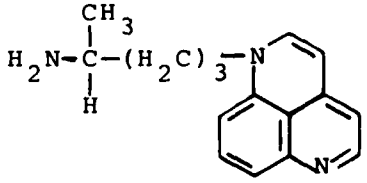
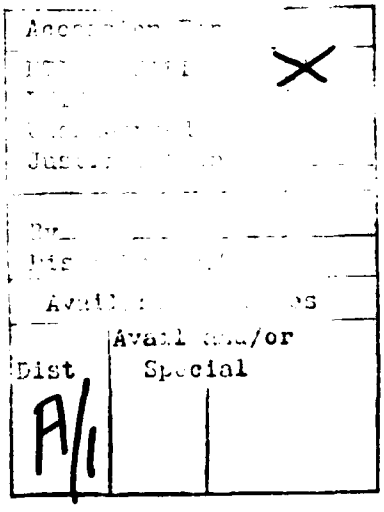


14 • 2HCl

the preparation of the target 17. The reaction of 1,6-diazaphenalene with singlet oxygen and peracids has also been determined as well as preparation of several key derivatives in the 9-methoxy-series.



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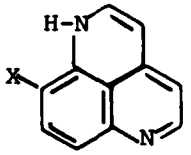
Contract No. DAMD17-78-C-8003

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

SUMMARY

The synthesis of the new "imidzaole-like" heterocycle 1,6-diazaphenalene 8 is described. The synthesis, from cyclohexane -1,3-dione 1 and dimethyl β-ketoglutarate 2, provides 40-60 grams of 8 with relative ease. In addition, the preparation of 9-methoxy-1,6-diazaphenalene (34) from ethyl acetoacetate and p-anisidine has been completed.

In order to develop reasonable routes to 7-amino-substituted 1,6-diazaphenalenes, an investigation of the reaction of 8 with electrophiles was undertaken. It was found that 8 reacts in acidic solution with electrophiles at position -7; however, attack, in neutral media, occurs at the 2,3,4 and 7-positions of 8. This discovery led to the preparation of several 7-substituted -1,6-diazaphenalenes including the 7-nitro 15, 7-bromo 16, 7-iodo 17, 7-chloro and 7-phenyldiazo species.



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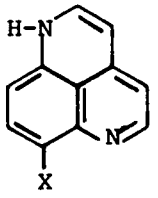

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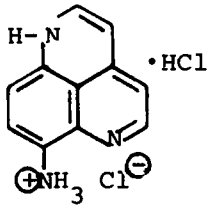

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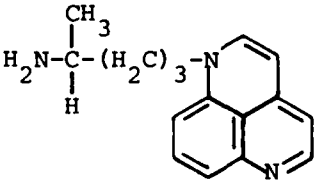


14 •2HCl

In addition, conditions have been found under which 8 has been N-alkylated with either benzylbromide or methyliodide to give N-alkyl analogs such as N-methyl-1,6-diazaphenalene (26). This result has recently led to the preparation of the target 14. Extension of this technology has permitted conversion of 9-methoxy-1,6-diazaphenalene 34 into the corresponding N-methyl derivative 39 and should permit preparation of target compounds in the 9-methoxy series (work in progress by Mr. Robert Weber).

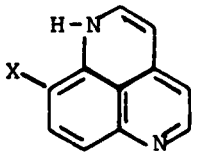
From the conception of the synthetic route to diazaphenalenes, it was felt the route to the 9-methoxy series should provide access to a number of substituted diazaphenalenes not easily obtainable by direct functionalization of the parent heterocycle. Extension of our dianion technology has been successfully employed to prepare 9-methoxy-2-substituted derivatives from dianion 31 and esters such as ethylbenzoate (see 42). Finally, 8 has been tested with either singlet oxygen or peracids to provide a variety of diazaphenalenones (enones) such as those depicted in Scheme IV. These α-β unsaturated ketones may provide an entirely different route to the targets of interest in this study.

FOREWORD

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.

This report contains a table of compounds which have been submitted and screened for antimalarial activity. In addition, a list of publications which were a direct result of this work is enclosed, as well as a summary of the personnel who worked under the contract.

In a chemical sense, the synthesis of the key diazaphenalenes



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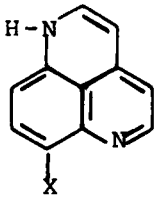

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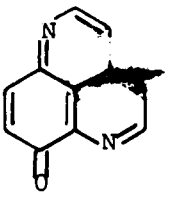
16, X = Br
17, X = I



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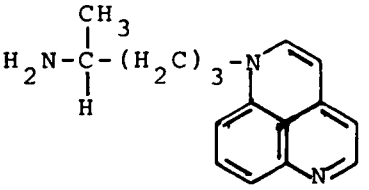

14 •2HCl

8 and 34 are presented, as well as a survey of the chemistry carried out, to date, on 8. This includes incorporation of amino, nitro, halo, and oxo functionality (see 10,15,16,17 and 27a) into position -7 of 8, furthermore, conditions have been found under which 8 was alkylated to provide the target compound 14. The chemistry of 9-methoxy-1,6-diazaphenalene has been explored briefly and is reported; this includes reactions of 34 with alkylating agents and some electrophiles. Work is in progress to convert 34 to the target compounds. The last portion of the report is a detailed experimental section.

Table of Contents

Targets and Intermediates Submitted to Walter Reed Army Institute of Research Contract DAMD17-78-C-8003

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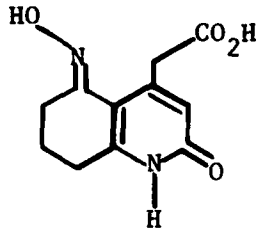
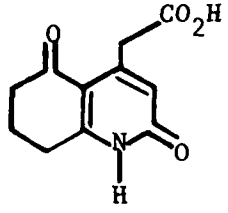
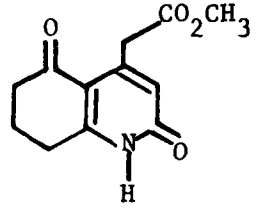
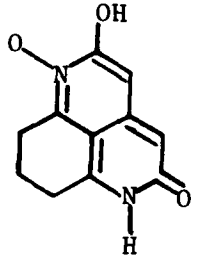
	BH64824	500 mg	Annual Summary Report (August 1978), p. 28.
	BH56966	500 mg	J. Oehldrich and J.M. Cook, J. Org. Chem., 42, 889 (1977); p. 893.
	BH56957	600 mg	J. Oehldrich and J.M. Cook, J. Org. Chem., 42, 889 (1977); p. 893.
	BH56948	350 mg	Annual Summary Report (August 1978), p. 29.

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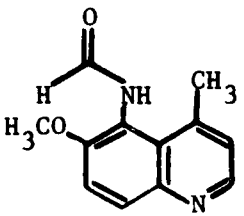
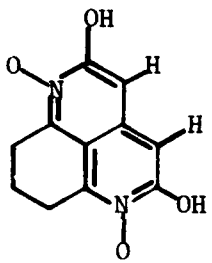
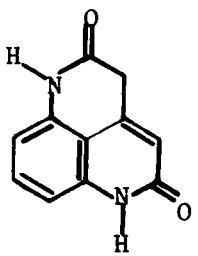
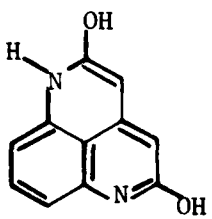
	BH73038	300 mg	Annual Summary Report (August, 1978), p. 27
	BH73047	400 mg	Annual Summary Report (August, 1978), p. 30.
	BH81601	330 mg	Annual Summary Report (August, 1978), p. 32-33.
	BH 81638	350 mg	Annual Summary Report (August, 1978), p. 33.

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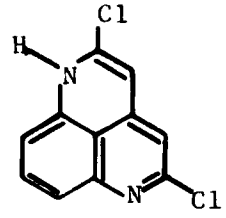
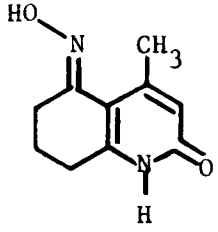
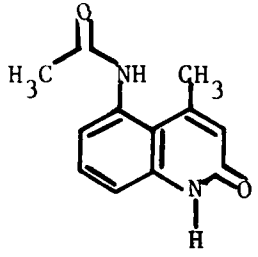
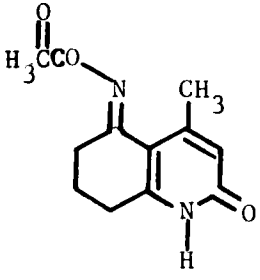
	BH84237	400 mg	J.-C. Chang, J.M. Cook et al. J. Org. Chem., 46, 4188 (1981); p. 4193.
	BH64780	400 mg	M.I. El-Sheikh and J.M. Cook, J. Org. Chem., 45, 2585 (1980); p. 2586.
	BH64799	400 mg	M.I. El-Sheikh and J.M. Cook, J. Org. Chem., 45, 2585 (1980); p. 2587.
	BH64806	200 mg	M.I. El-Sheikh and J.M. Cook, J. Org. Chem., 45, 2585 (1980); p. 2587.

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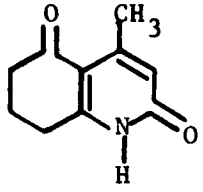
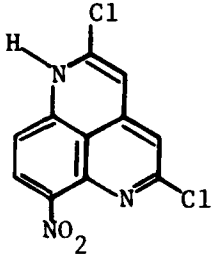
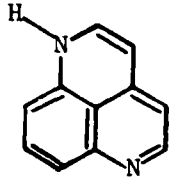
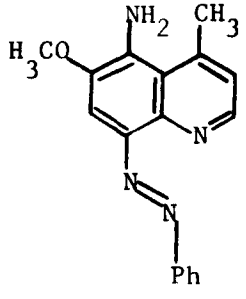
	BH64815	400 mg	M.I. El-Sheikh, and J.M. Cook, J. Org. Chem., 45, 2585 (1980); p. 2586.
	BJ34081	500 mg	Annual Summary Report, January 1979 to December 1979; p.18.
	BJ34090	500 mg	J.C. Chang, J.M. Cook et al., J. Org. Chem., 46, 4188 (1981); p. 4193.
	BJ34063	500 mg	Annual Summary Report, January 1979 to December 1979, p. 21.

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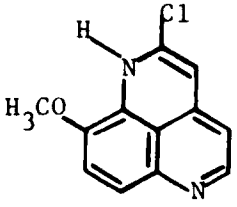
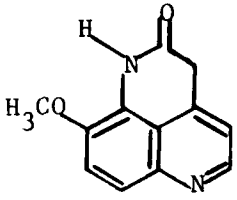
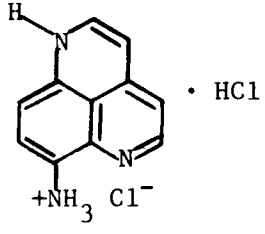
	BJ34072	500 mg	Annual Summary Report, January 1979 to December 1979, p. 19.
	BJ34296	500 mg	Annual Summary Report, January 1979 to December 1979, and Final Report, p. 9.
	BJ59088	500 mg	Annual Summary Report, January 1979 to December 1979, p. 18.

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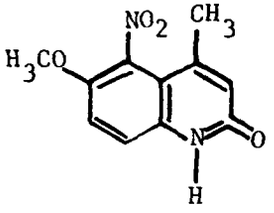
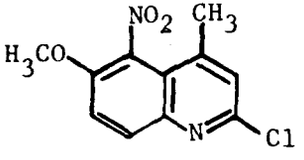
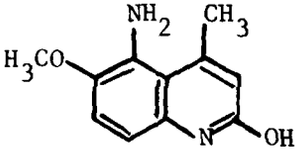
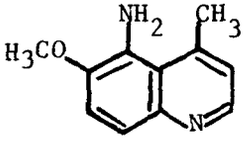
	BH56984	500 mg	Annual Summary Report (August 1978), p. 26.
	BH56975	500 mg	Annual Summary Report (August 1978), p. 27.
	BH56993	500 mg	Final report p. 9.
	BH73056	500 mg	Annual Summary Report (August 1978), p. 27.
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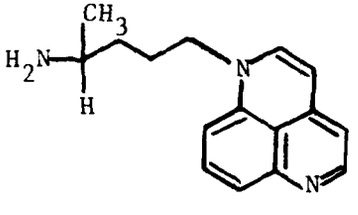
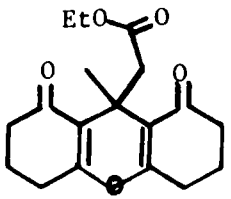
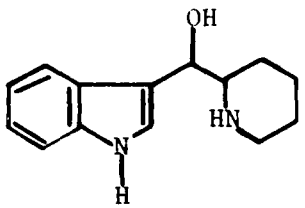
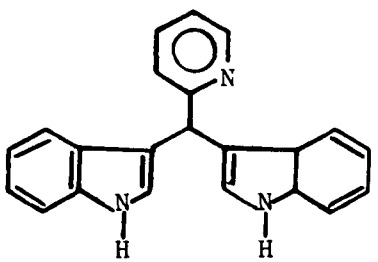
 • 2HCl	BJ86012	400 mg	Annual Summary Report (January 1981 to December 1981). p. 36.

Structure	Bottle Number	Amount	Reference
Gift Compounds			
	BH56939	1 gram	J. Oehldrich and J.M. Cook, J. Org. Chem., 42, 889 (1977); p. 893.
	BH57007	500 mg	O. Campos, Ph.D. Thesis, University of Wisconsin-Milwaukee, (1978), p. 141.
	BH84504	630 mg	O. Campos, Ph.D. Thesis, University of Wisconsin-Milwaukee, (1978), p. 132.

Work in Progress

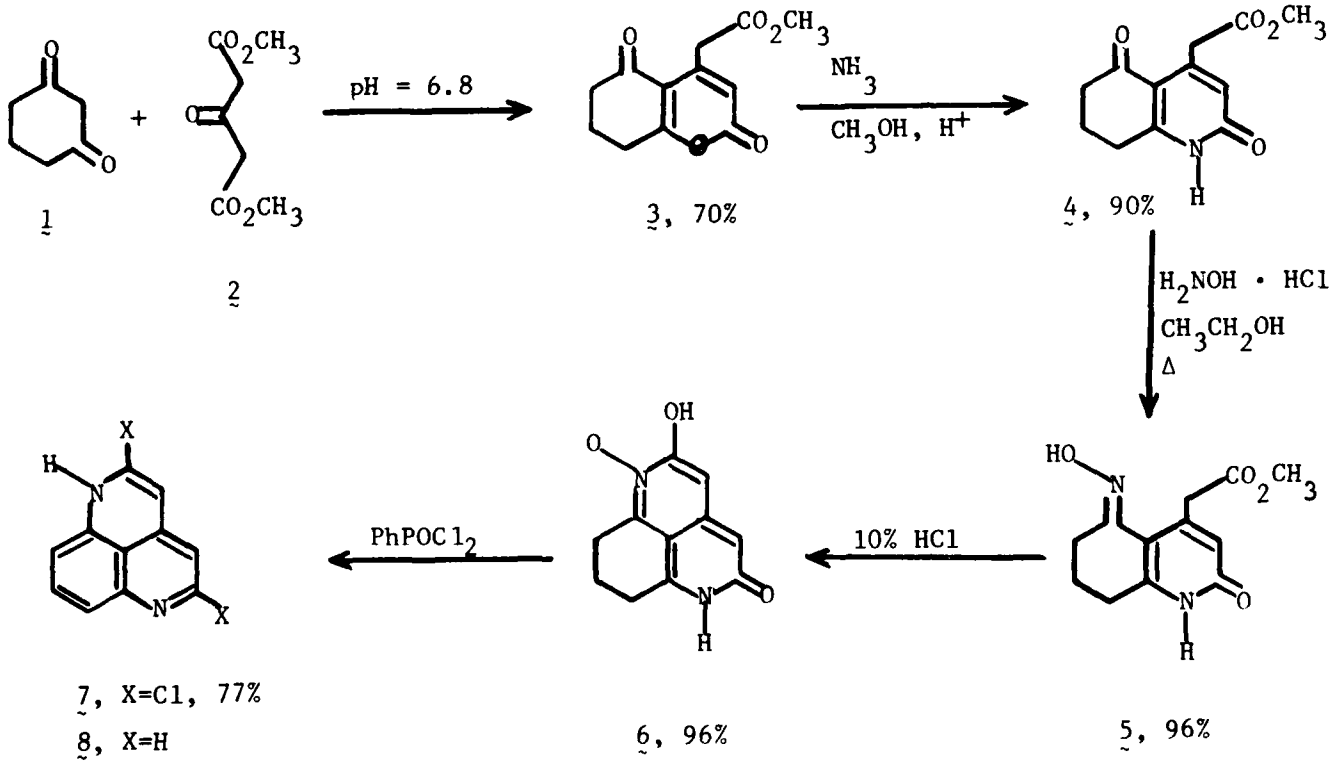
This report is divided into sections A and B the first of which deals with the synthesis of 1,6-diazaphenalene (8), and a study of the chemistry of this molecule. Part B concerns itself with the preparation and chemistry of the 9-methoxy analogs (34) of 1,6-diazaphenalene.

A. The synthesis of 1,6-diazaphenalene (8) was successfully completed in six steps from the readily available cyclohexane-1,3-dione (1) and dimethyl 3-keto-glutarate (2).[1] The yields are illustrated in Scheme I, and a description of the preparation has been outlined in the Annual Report (see reference 1 for details).

The intermediate (7) from this work was then nitrated ($NaNO_2$, CF_3COOH) at -60°C, as illustrated in Scheme II, to provide the desired 7-nitro-2,5-dichloro-1,6-diazaphenalene (9) in good yield. This nitro derivative was subjected to catalytic hydrogenation to give 7-amino-1,6-diazaphenalene 10 as a stable dihydrochloride salt. All attempts, however, to convert this salt into the free base 11 gave only products of decomposition presumably via oxidation to 12 followed by fragmentation.

Scheme I

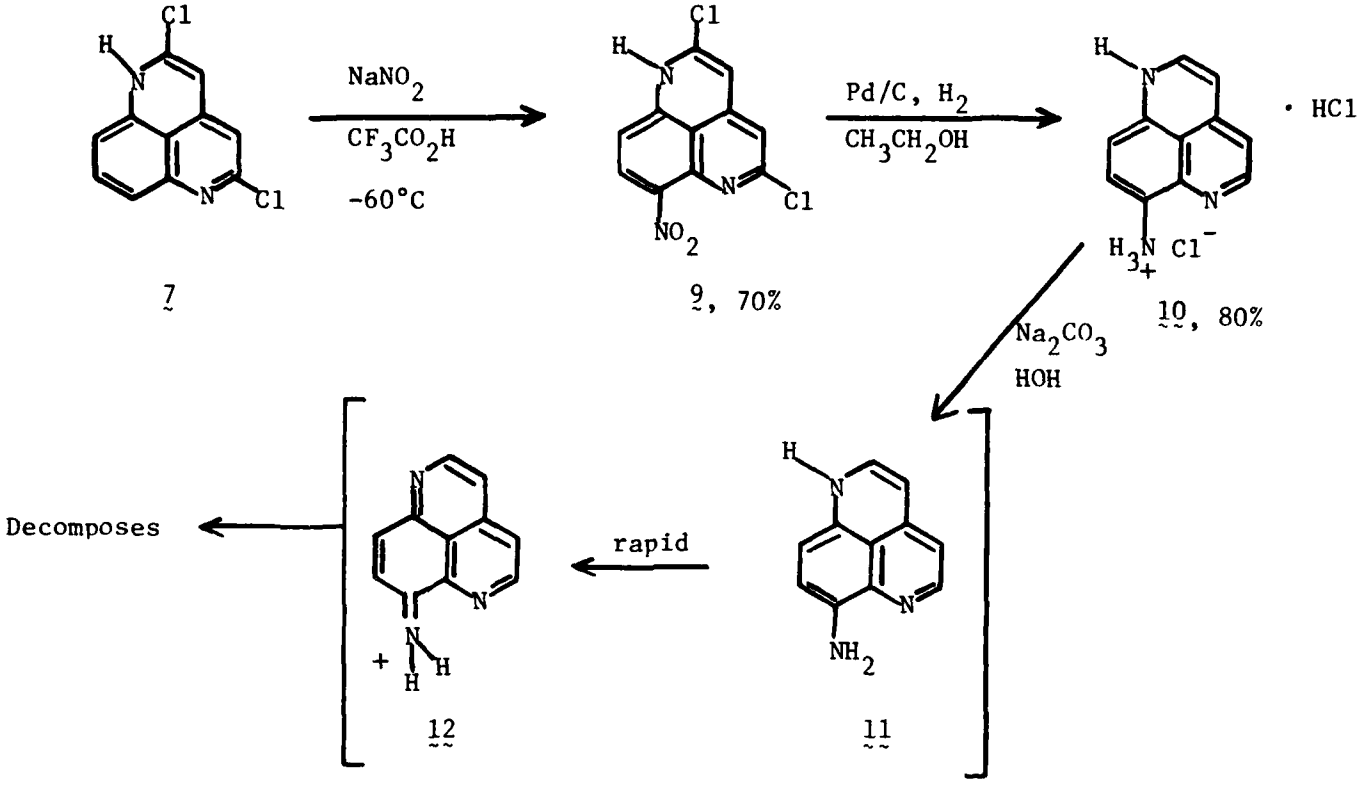
Synthesis of 1,6-Diazaphenalene 8[1]



See Annual Report 1978 and J.C. Chang and J.M. Cook et al. J. Org. Chem., 46, 4188-4193 (1981) for details.

Scheme II

Synthesis of 7-Amino-1,6-Diazaphenalene Dihydrochloride 10



7

9, 70%

10, 80%

12

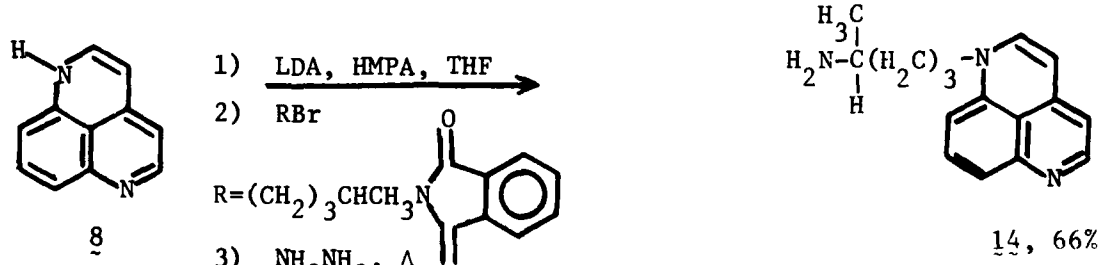
11

See Annual Report 1979 for details.

Attempts to circumvent the lability of 11 were numerous, and resulted in the synthesis of several 1-alkyl-1,6-diazaphenalenes. One of these experiments led to the preparation of the target 14, as depicted in Scheme III. Along these

Scheme III

Alkylation of 1,6-Diazaphenalene to Provide Target 14[3]



8

13

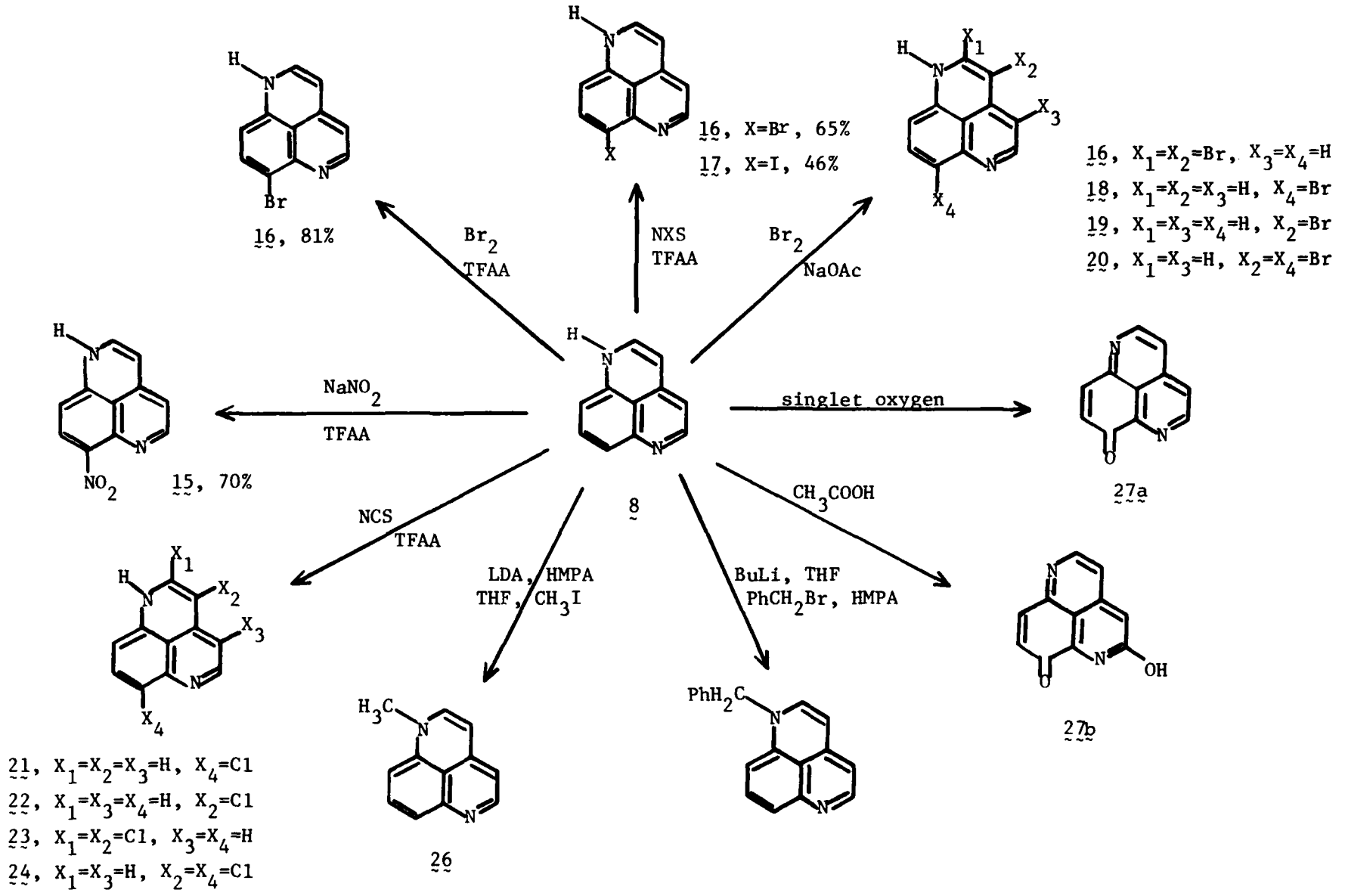
14, 66%

See Annual Report 1980; K. Avasthi, J.M. Cook et al., Heterocycles, 16, 1453 (1981). S.-J. Lee and J.M. Cook, Heterocycles, 16, 2125 (1981) for details.

same lines a detailed investigation of the chemistry of 1,6-diazaphenalenes (8) was carried out. Some of the reactions 8 underwent are illustrated in Scheme IV.

Scheme IV

Reactions of 1,6-Diazaphenalene (8)[3]

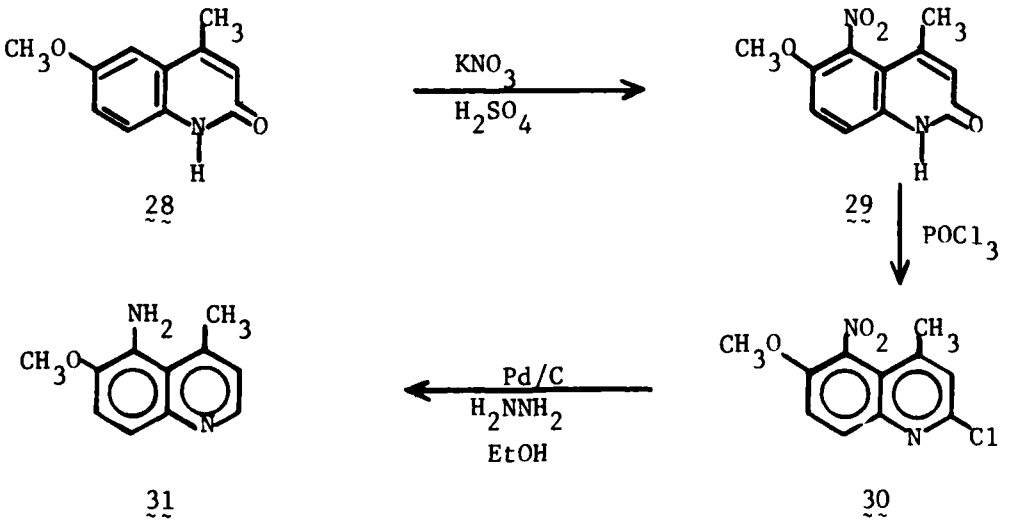


See Annual Report, 1980; K. Avasthi, J.M. Cook et al., Heterocycles, 16, 1453 (1981), S.-J. Lee and J.M. Cook, Heterocycles, 16, 2125 (1981) for details.

A complete description of the research on 1,6-diazaphenalene (8) is detailed in the three Annual Reports (1978, 1979, 1980), and will not be repeated here; however, recent research on 9-methoxy-1,6-diazaphenalene will be discussed.

During work directed toward preparation of targets which contain the 9-methoxy group some alterations in the previously reported procedures were made to permit the preparation of key intermediates on large scale. Nitration of 2-hydroxy-6-methoxylepidine (28), according to the published procedure[4] ("nitrous vapors"), was effective on small scale but was not suitable for the preparation of large quantities of (29). It was found that nitration of (28) with KNO_3/H_2SO_4, a procedure which has been successfully employed for the nitration of several similar quinoline derivatives[5], could be carried out efficiently at the 100 g level (see Scheme V). The large scale conversion of the nitroquinolone (29) into the 2-chloro derivative (30) was readily carried out by treatment with hot $POCl_3$. Hydrogenolysis of the chloro functionality with concurrent reduction of the nitro groups was best performed using Pd/C and hydrazine in refluxing ethanol. This afforded the 5-amino quinoline 31; the sequence is outlined in Scheme V.

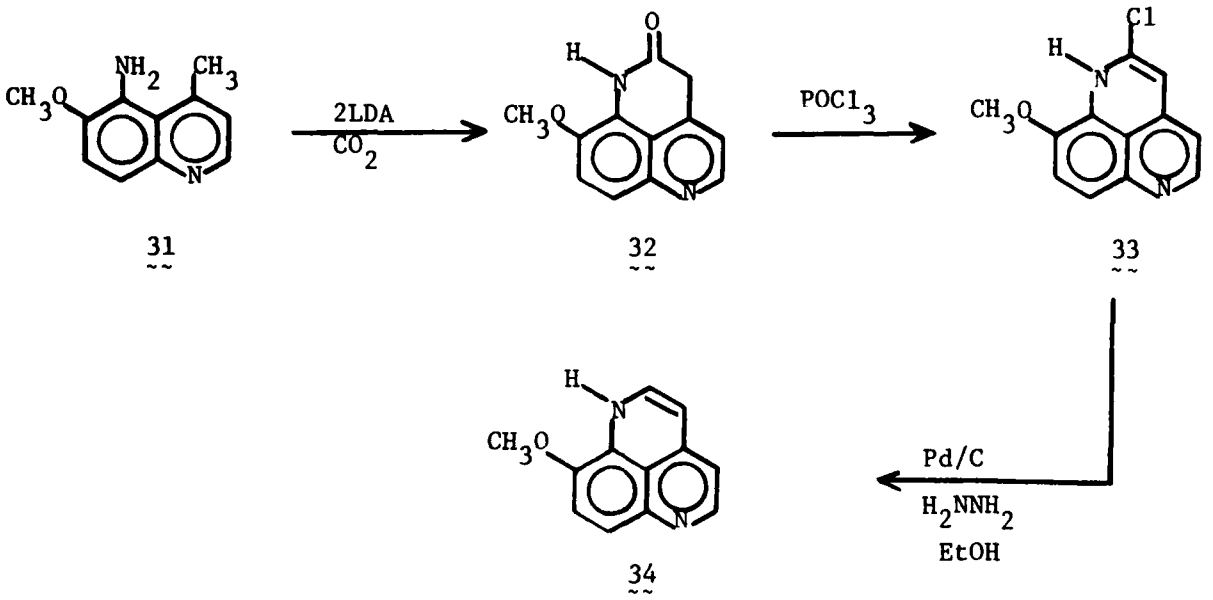
Scheme V



Construction of the third ring was accomplished by generation of the dianion of (31) with two equivalents of LDA followed by carbonylation to yield the tricyclic lactam (32). This compound was readily converted to chloro-methoxy-1,6-diazaphenalene (34) on treatment with hot $POCl_3$, followed by hydrogenolysis, as

shown in Scheme VI.

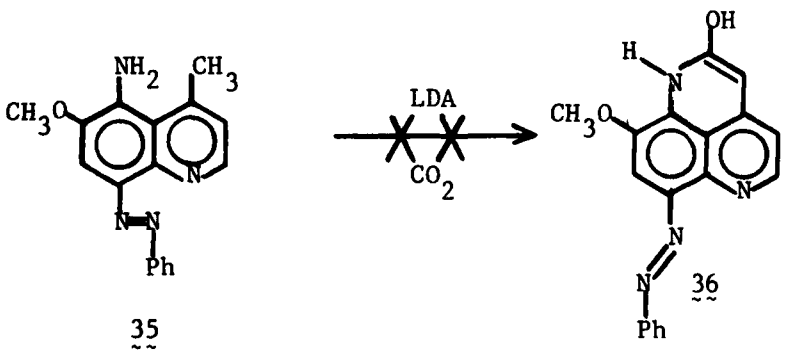
Scheme VI



31 32 33 34

The properties of (34) are similar to those of the parent heterocycle (8, polar molecule, low solubility in common organic solvents) with the exception of the proton nmr spectrum. Here, incorporation of the methoxy group resulted in loss of symmetry, as compared to (8), and one observed a spectrum consisting of 6-doublets, as expected.

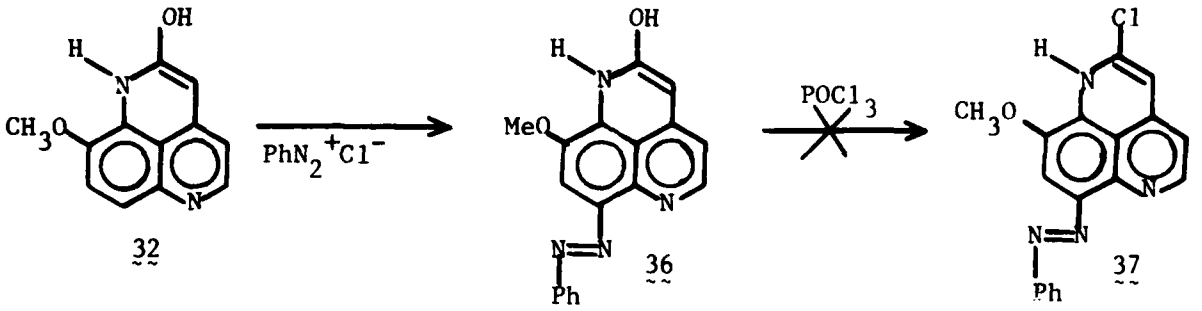
Next, efforts were directed toward incorporation of an amino group in the 7 position of 34. A previous Annual Report detailed the preparation of the 8-phenylazo quinoline (35) and the attempted conversion to (36). It was found that lactam 32 could be readily coupled with phenyldiazonium chloride to



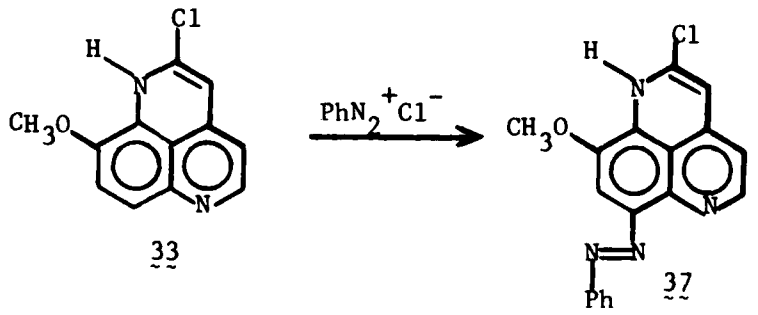
35 36

yield (36). With an authentic sample of (36) in hand it can now be established that no (36) was produced in any of the carbonylation reactions carried out on

the dianion of (35). Surprisingly, (36) proved resistant to prolonged heating with $POCl_3$, and all attempts to convert (36) to the 2-chloro derivative, (37) returned only starting material. The 2-chloro-9-methoxy-1,6-diazaphena-

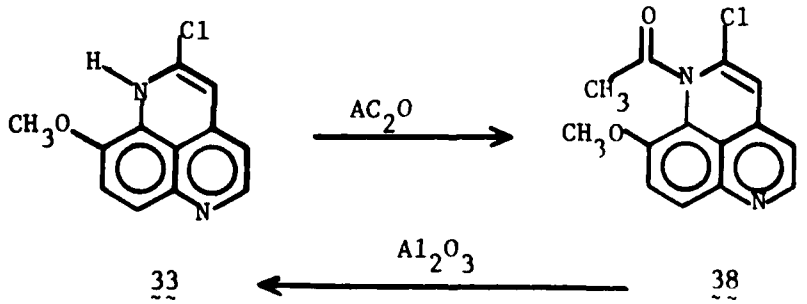


lene (33) was found to couple smoothly with phenyl diazonium chloride to provide (37). At this point a search for the proper conditions for reduction of the azo

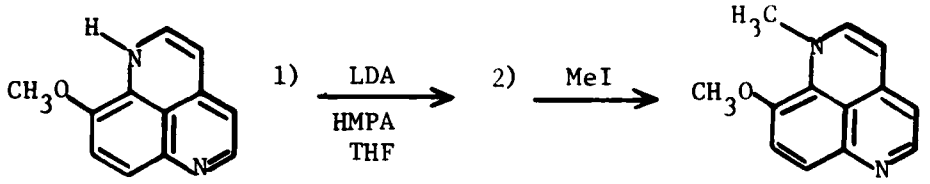


group of these intermediates to afford the desired 7-amino-9-methoxy-1,6-diazaphenalene will be carried out for it appears that the same factors which render (11) unstable are also operating in these cases.

In an attempt to prepare a more stable diazaphenalene, the acetate of (33) was synthesized by refluxing the material in acetic anhydride. While this compound (38) was stable to dilute aqueous base, it reverted back to (33) upon chromatography on alumina.

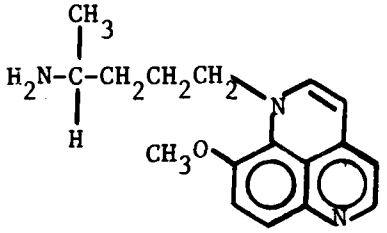


The N-alkylation of (34) under conditions analogous to those employed to alkylate (8) has been examined. Consequently, treatment of (34) with LDA, THF, HMPA followed by MeI afforded the N-methyl derivative (39) in good yield.

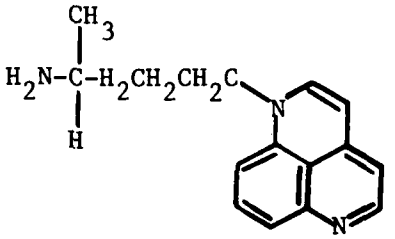


34 39

The alkylation of (34) with the appropriate halides to afford targets such as (40) is currently under investigation. Due to the hydroscopic nature



40



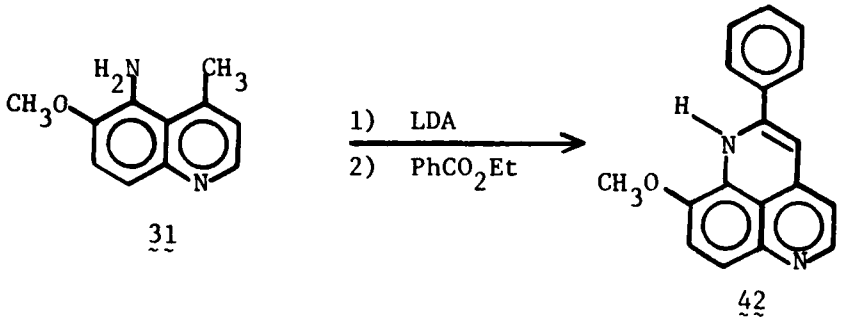
41

(See Annual Report, 1981)

of the dihydrochloride of target 41, the oxylate salts will be prepared in this series.

From the conception of the synthetic route to diazaphenalenes outlined in Scheme VI, it was felt that this route should permit the synthesis of a number of substituted diazaphenalenes not obtainable by direct functionalization of the parent heterocycle (8).

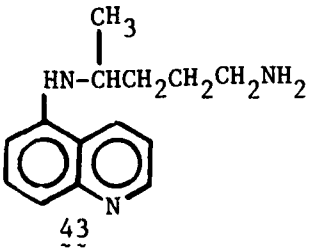
The requirements here being an amino group at the 5 position, an alkyl function at the 4- position, and any other functionality unaffected by the carbonylation conditions. In this vein, recently, a study of the reactivity of the dianion of (31) toward various electrophiles (other than CO_2) was begun. When the dianion of (31) was quenched with ethyl benzoate, 2-phenyl-9-methoxy-1,6-diazaphenalene (42) was obtained. This sequence appears to work best when non-enolizable esters are employed.



31 42

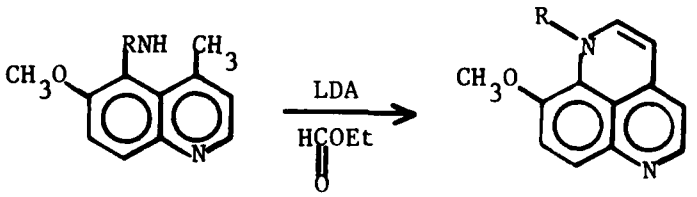
When (31) was treated with 2 eq. LDA followed by ethyl formate, 9-methoxy-1,6-diazaphenalene (34) was formed directly, making this heterocycle available in six steps from ethyl acetoacetate and p-anisidine. The optimization of reaction conditions and scale up of this reaction are currently under study.

A recent report describing the antimalarial activity of the 5-amino quinoline (43)[6] prompted us to consider preparation of derivatives of (31) in which the methyl and methoxy groups are in the same positions as the active drug 4-methyl primaquine.



43

This work is underway and the intermediates will be screened, and then converted into the target diazaphenalenes in one step as illustrated below.



R = antimalarial side chain

EXPERIMENTAL

Microanalyses were performed on an F & M Scientific Corporation Carbon, Hydrogen, Nitrogen Analyzer Model 185; some analyses were carried out at the National Institutes of Health, Bethesda, Maryland. Melting points were taken on a Thomas Hoover melting point apparatus; they are uncorrected. Nuclear Magnetic Resonance spectra were recorded on Varian T-60, HA-100, and CFT-20 spectrometers while infrared spectra were recorded on a Beckman Acculab-1

instrument. Mass spectra were taken on either a Hitachi Perkin-Elmer RMU-6 or Hewlett Packard 5855 GC/MS. High pressure liquid chromatography was performed on a Waters Preparative LC-500 Liquid Chromatograph. Analytical TLC plates employed in this work were Merck-Brinkmann UV active silica gel G on plastic.

2-Hydroxy-4-methyl-5-nitro-6-methoxy quinoline 29.

To a cooled (ice-water bath) solution of 2-hydroxy-4-methyl-6-methoxy quinoline 28 (70.50 g, .373 mol) in H_2SO_4 (350 ml, conc) was added potassium nitrate (41.50 g, .410 mol) in portions over one hour with stirring (mechanical). The solution was allowed to come to room temp. and stirring was continued for twelve hr. The solution was then poured into a 2 L beaker of ice after which the nitro compound 29 precipitated. The crude product was collected by filtration suspended in water (400 ml), and brought to pH > 8 with 14% aq. NH_3. The precipitate which remained was recrystallized from ethyl acetate to afford the pure nitro derivative 29 (74.5 g, 85%): mp 298-300°C (lit 278-280)[7]; ir (KBr), 1690, 1650, 1520, 1275 cm^{-1}. NMR (CF_3COOH) δ2.73 (s, 3H, CH_3) 4.10 (s, 3H, OCH_3) 7.20 (s, -1 H arom) 7.77 (d, J=8Hz, 1H arom) 8.00 (d, J=8Hz, 1H arom); mass spectrum (E.I.) 234 (M^+, 100), 160(55), 145(45), 130(62), 117(52).

2-Hydroxy-4-methyl-5-amino-6-methoxy quinoline (31).

A mixture of 29 (1.0 g, 0.004 mol) and Zn (2.5 g) in glacial acetic acid (20 ml) was refluxed for 2 hrs, after which the solution was cooled and filtered. The mother liquor was diluted with water (30 ml) to precipitate 31 which was collected by filtration and recrystallized from ethanol to yield the amino derivative 31 (0.64 g, 72%): mp 270-271°C (lit 270-272°C).[4]

2-Hydroxy-9-methoxy-1,6-diazaphenalene 32

A solution of LDA was prepared by addition of diisopropyl amine (7.07 g, 0.07 mol) in THF (50 ml) to nBuLi (54 ml of 1.3 M solution in hexane, 0.07 mol) at -78°C, under N_2. After stirring for 20 min, the amine 31 (5.64 g, 0.03 mol) in 100 ml THF was added dropwise with stirring. The deep red solution which resulted was stirred for one hour and then poured into a large excess of pulverized dry ice. Saturated NH_4Cl solution (100 ml) was added after the dry ice, which remained, had vaporized and the organic layer was separated from the aqueous phase. The product crystallized from the aqueous phase to yield 32 (5.4 g, 84%): mp 253-255°C; ir (KBr) 3230 (b), 1640, 1580, 1250, cm^{-1}; NMR (DMSO-d_6) δ3.88 (3H, s, OCH_3), 5.32 (1H, s), 5.62 (1H, d, J=7Hz), 6.55 (1H, d, J=8Hz), 7.01 (1H, d, J=7Hz) 7.10 (1H, d, J=8Hz); mass spectrum (C.I., CH_4) 215

(P+1, 100).

2-Chloro-9-methoxy-1,6-diazaphenalene 33.

A mixture of 2-hydroxy-9-methoxy-1,6-diazaphenalene (32, 5.0 g, 0.023 mol) and $POCl_3$ (20 ml) was heated for 2 hrs with a hot water bath (boiling). The solution was then allowed to cool. The excess $POCl_3$ was removed under reduced pressure, and the residue poured onto ice. The slurry which resulted was brought to pH > 8 with NH_3 (14%, aqueous). The solid which precipitated was collected by filtration to give 33 (5.1 g, 94%): mp 228-232°C. An analytical sample was prepared by washing 33 through a short column of alumina (5% MeOH, CH_2Cl_2); ir (KBr) 3240, 1620, 1540, 1280, 1250, 1120 cm^{-1}; NMR (DMSO d_6) δ3.82 (3H, s, OCH_3) 5.70 (1H, d, J=7Hz), 6.25 (1H, s), 6.61 (1H, d, J=8Hz), 7.04 (1H, d, J=7Hz), 7.12 (1H, d, J=8Hz); mass spectrum (C.I., CH_4) 233 (P+1, 100).

Anal. Calcd. for $C_{12}H_9N_2OCl$: C: 62.07, H: 3.88, N: 12.07. Found: C: 62.38, H: 3.94, N: 11.66.

9-Methoxy-1,6-diazaphenalene 34.

A mixture of 2-chloro-9-methoxy-1,6-diazaphenalene (33, 0.86 g, 0.003 mol), Pd/C (0.2 g, 10%) in 95% ethanol (60 ml), and hydrazine (4 ml) was refluxed for 6 hrs. The mixture was then cooled and filtered. The solvent which remained was removed under reduced pressure, and the residue was treated with K_2CO_3 (aq solution). The product (34) which precipitated was collected by filtration to yield 0.51 g (70%): mp 192-194°C; ir (KBr) 1600, 1550, 1330, 1220 cm^{-1}; NMR (DMSO-d_6) δ3.81 (3H, s, OCH_3), 5.82 (1H, d, J=6Hz), 5.97 (1H, d, J=6Hz), 6.78 (1H, d, J=8Hz) 7.18 (2H, 2d, superimposed), 7.65 (1H, d, J=6Hz); mass spectrum (C.I., CH_4) 199 (P+1, 100%).

2-Hydroxy-7-phenylazo-9-methoxy-1,6-diazaphenalene (36).

A solution of (32, 0.50 g, 0.0023 mol) in water (40 ml), glacial acetic acid (15 ml), and saturated NaOAc (20 ml) was cooled to 0°C with stirring. A solution of phenyldiazonium chloride was prepared by dissolving aniline (0.21 g, .0023 mol) in 1NHCl (8 ml) followed by the addition of $NaNO_2$ (1N, 2.1 ml) with chilling. The solution of the diazonium salt was then added dropwise to the solution of (32), after which stirring was continued for 1/2 hr. The dark blue solution was brought to pH > 8, and extracted with CH_2Cl_2. The organic phase was dried (K_2CO_3), and the solvent was removed under reduced pressure to afford 36 as a red solid (0.71 g, 97%): mp 210-215 (dec); ir (KBr) 3200, 1630, 1500, 1230, 1210 cm^{-1}; NMR ($CDCl_3$) δ3.94 (3H, s, OCH_3), 7.16-7.50 (8H, m), 7.71 (1H, d, J=5Hz); mass spectrum (C.I., NH_3) 319 (P+1, 100).

Anal. Calcd. for $C_{18}H_{14}N_4O_2$: C; 67.92, H, 4.40, N, 17.61. Found: C, 68.38, H, 4.47, N, 17.08.

2-Chloro-7-phenylazo-9-methoxy-1,6-diazaphenalene (37).

To a solution of (33, 1.5 g, 0.0065 mol) in water (80 ml) and acetic acid (20 ml) at 0°C was added dropwise a solution of phenyldiazonium chloride [0.0065 mol, from aniline (0.60 g) in HCl (1N, 15 ml) and $NaNO_2$ (1N, 6.5 ml)]. The reaction was allowed to stir at 0° for an additional 1 hr followed by stirring at room temp for 3 hr. The solution was brought to pH > 8 with NH_3 (14% aq) after which the product precipitated and was collected by filtration to give 37 (1.32 g, 60%): mp 217-219°C; ir (KBr) 1600, 1560, 1520, 1500, 1310, 1250, 1200 cm^{-1}; NMR ($CDCl_3$) δ3.93 (3H, s, OCH_3), 6.70-7.60 (8H, m) 8.02 (1H, d, J=5Hz); mass spectrum (C.I., NH_3) 337 (P+1, 100).

1-Methyl-9-methoxy-1,6-diazaphenalene (39).

To a solution at -78°C of LDA (0.00083 mol in 10 ml THF) prepared in the usual manner under N_2, was added 9-methoxy-1,6-diazaphenalene (34, 0.15 g, 0.00076 mol) in 10 ml THF to which HMPA (0.5 ml) had been added. After stirring for 20 min, methyl iodide, [0.12 g (0.00083 mol)] in 5 ml THF was added, and the reaction was allowed to come to room temp. Water (20 ml) was added and the mixture was extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to yield the N-methyl compound 39 (0.11 g, 68%: mp 151°C; ir (KBr) 2940, 1610, 1580, 1490, 1330, 1240 cm^{-1}; NMR ($CDCl_3$) δ3.19 (3H, s, N-CH_3), 3.98 (3H, s, OCH_3), 5.64 (1H, d, J=7Hz), 6.13 (1H, d, J=8Hz), 6.36 (1H, d, J=5Hz), 6.60 (1H, d, J=7Hz) 6.92 (1H, d, J=8Hz), 8.31 (1H, d, J=5Hz); mass spectrum. (C.I. CH_4) 213 (P+1, 100).

2-Phenyl-9-methoxy-1,6-diazaphenalene (42).

To a solution at -78°C of LDA (0.0058 mol) in THF (5 ml) under N_2 was added dropwise the amine (31, 0.50 g, 0.0026 mol) in 10 ml THF. Stirring was continued for 2- min after which ethyl benzoate [0.48 g (0.0032 mol)] in THF (5 ml) was added. The solution was allowed to come to room temp. whereupon stirring was continued for 1 hr. Water (10 ml) was added and the precipitate which formed was collected by filtration and washed through a short column of alumina (CH_2Cl_2) to afford pure 42 (0.29 g, 41%): mp 184°C; ir (KBr) 2900 (b), 1600, 1530, 1430, 1340, 1270, 1220 cm^{-1}; NMR ($CDCl_3$) δ3.92 (3H, s, OCH_3), 6.08 (s, 1H), 6.16 (d, 1H, J=5Hz), 7.10-7.80 (7H, m), 7.92 (1H, d, J=5Hz); mass spectrum (C.I., CH_4) 275 (P+1, 100).

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2. See Annual Report 1979 for details.

3. K. Avasthi, J.M. Cook et al., Heterocycles, 16, 1453 (1981), S.-J. Lee and J.M. Cook Heterocycles, 16, 2125 (1981) and Annual Report 1980 for details.

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