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# Substituted ℓ-dialkylaminomethyl-3-phenyl-1-naphthalenemethanols

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# SUBSTITUTED

# α-DIALKYLAMINOMETHYL-3-PHENYL-1-NAPHTHALENEMETHANOLS

BY

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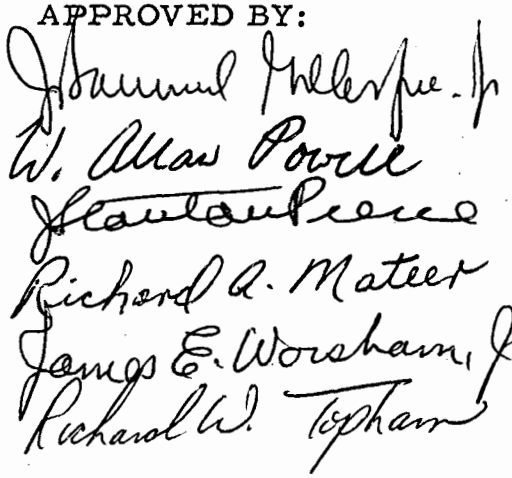

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# INTRODUCTION

Malaria is still a world health problem. Established antimalarial drugs have become ineffective in many areas because of the emergence of resistant strains of malaria. New efforts have been initiated to study variations of new untried compounds and earlier structures shown to have activity. The 4-quinolinemethanols fall into the latter class. The great activity of the 4-quinolinemethanols is offset by their phototoxic activity.

The possibility that substituted $\alpha$-dialkylaminomethyl-3-phenyl-1-naphthalenemethanols, as analogs of the 4-quinolinemethanols, would be effective antimalarials, yet not have the phototoxic side effect, is discussed in this paper. Synthetic pathways to the naphthalenemethanols are discussed. Experimental procedures are given to obtain some of the target compounds. A discussion is made of the procedures including problems encountered.

# HISTORICAL

## Background

"It is sufficient to say that the continued intelligent and skilled uses of the newer methods of mosquito control and the proper use of new antimalarial drugs will go far in reducing the menace of malaria to that of a minor tropical disease." (1) Statements such as this by knowledgeable sources were common as late as the early 1950's. The efficacy of such drugs such as Quinacrine, Chloroquine, and Primaquine appeared satisfactory for prophylaxis and therapy of malaria (2). As a result, the huge, expensive, and concerted efforts of this and other countries during World War II rapidly subsided.

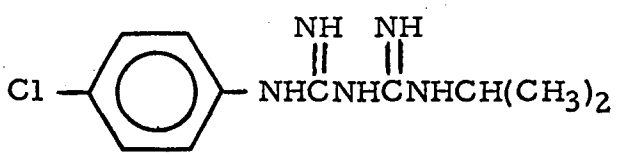
However, by the early 1960's, disquieting reports of refractory strains began to appear (3). Within a few years, strains of Plasmodium falciparum appeared that were resistant to so many of the available antimalarials it became necessary to return to quinine for effective control (4). The problem was of sufficient magnitude to the United States Armed Forces in Southeast Asia that new government programs were enacted to

search for, and study the problems of, antimalarial drugs (5).

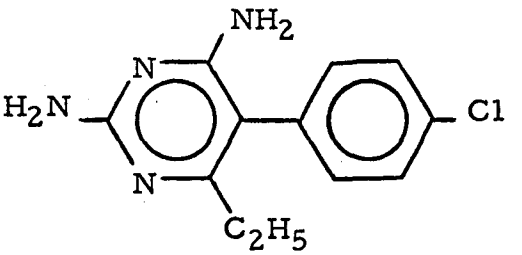
Antimalarials are divided into two general categories according to their proposed metabolic mechanisms (6). The first category is the metabolic antagonists of folic acid. Classic examples are the compounds chlorguanide, 1, and Daraprim, 2. Antifolics are often excellent antimalarials when used against susceptible strains. However, they suffer two drawbacks. First, they react too slowly to be of use in an acute malarial attack. Second, they readily induce drug resistance in the parasite.

The second category of antimalarials is the quinoline-acridine group, which operates by other metabolic processes. Examples of this group are quinine, 3, and pentaquine, 4. It is thought that these compounds interfere with nucleic acid synthesis. They are advantageous in that they do not induce parasite resistance readily, and they are useful in acute cases of malaria. However, they often show undesirable toxic effects.

Included in the second category are the compounds known as the 4-quinolinemethanols, simplifications of the quinine structure. An example of this type is 6,8-dichloro-2-phenyl-$\alpha$-2-piperidyl-4-quinolinemethanol, 5. Considerable interest was shown in this compound both because of its activity against malaria and its side effects. A large number of compounds of this type were synthesized during and immediately after World War II (7, 8, 9).



1



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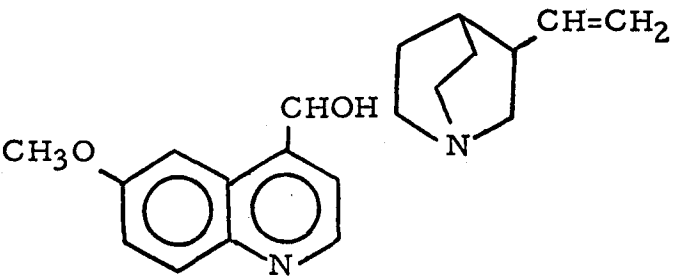

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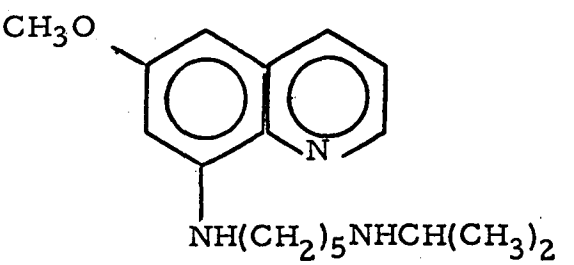

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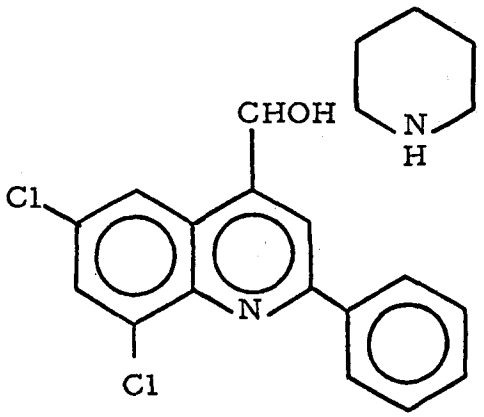


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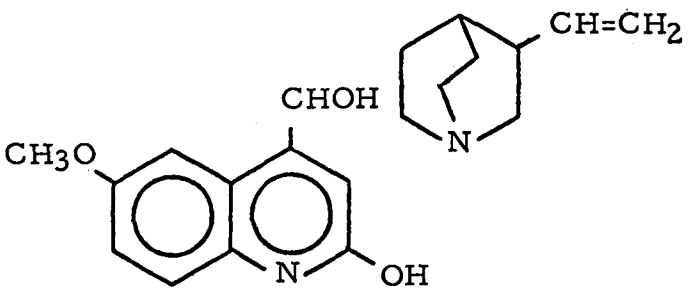


6

One of the most attractive qualities of the 4-quinolinemethanols has been their consistently significant activity against malarial infections in several species, including man (5, 10, 11). A wide variety of substitutions has resulted in good activity. One of the more important substitutions was the placing of certain suitable groups in the 2 position of the quinoline ring. The insertion of groups in the 2 position was prompted by the discovery that the first metabolic product of quinine in man and laboratory animals is the 2-hydroxy derivative, 6, of the parent compound (12). More study revealed that compound 6 had considerably less antimalarial activity than quinine (10). It was thought that the introduction of a blocking group in the 2 position would retard the metabolic oxidation of this class of compounds. This was indeed the case, and the introduction of a phenyl or p-chlorophenyl group into the 2 position of the quinoline ring caused highly significant increases in antimalarial activity of the 4-quinolinemethanols (10).

For all the efficacy the 4-quinolinemethanols have in the treatment of malaria, they possess the serious side effect of phototoxicity. Compound 5 caused severe photosensitization in human subjects for long periods after drug administration was stopped (10).

With the advent of the more recent programs renewed efforts were directed in the preparation of 4-quinolinemethanols in the hope of finding a structural modification that would retain good antimalarial activity without phototoxic side effects. Large numbers of variously

substituted compounds were made, including some prepared in this laboratory (13). Significant activity was demonstrated by many. However, they were phototoxic (14). The severity of phototoxic activity roughly paralleled antimalarial activity.

In an effort to alleviate phototoxicity, and still retain the activity of the quinolinemethanol system, the quinolinemethanol side chain was moved from the 4 position to other positions. For instance, some 8-quinolinemethanols were prepared in this laboratory (15). These compounds had significantly less activity than the 4-quinolinemethanols. Phototoxicity reappeared when there was significant activity.

## Purpose and Rationale

The question then arises as to what modification of the quinolinemethanol structure might retain significant antimalarial activity and not be phototoxic. This logically raises a second question: to what can

the phototoxicity of these compounds be attributed? At this time answers to the second question become conjecture at best. Rothe and Jacobus (14) suggested that three conditions are necessary for phototoxic activity. First, substitution of the quinoline ring in the 2 position is required. Second, substitution in the 5, 6, 7 and 8 positions of the quinoline nucleus increases phototoxicity. Third, the methanol side chain is important for toxicity. An obvious fact emerges from collected data. These are the very requirements for significant activity in the quinolinemethanols. However, it is possible that what is happening is an enhancement of an already basic property of the quinoline nucleus. Further, the basis of phototoxic activity might be due to the quinoline nitrogen itself.[1] This assumption made, one returns to the first question stated at the beginning of this section. What modification of the quinolinemethanol structure might retain significant antimalarial activity and not be phototoxic?

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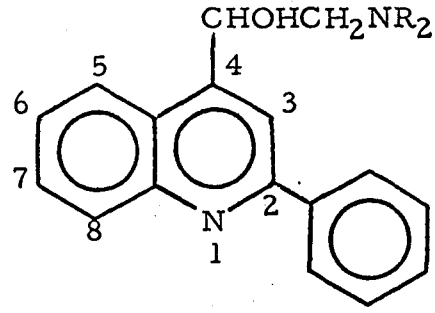
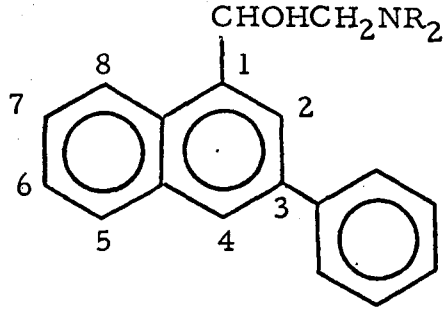
1. There is some rationale for this assumption. Many studies of phototoxicity (14, 17, 18, 19) indicate that uv radiation above 3200Å is responsible for the phototoxic reaction. I. G. Fels (20) showed that the drug itself, and not a metabolite, is most likely responsible for photoactivity. Examination of the uv spectra of a number of the 4-quinolinemethanols prepared in this laboratory show a medium intensity absorption band centered at 3400Å. Although no hard data exists, this band could be due to the n--$\pi^*$ transition of the quinoline nitrogen.

A logical answer is the substitution of -CH= in place of the -N=, i. e., the replacement of the quinoline system (Figure 1, a) with the naphthalene system (Figure 1, b). This replacement is considered an acceptable method of structure alteration for medicinals. The -CH= group is an isostere of -N=. According to Burger (16), molecules or molecular fragments containing an identical number and arrangement of electrons have similar properties. The greatest similarity exists when the isosteres are isoelectric. The -CH= and -N= fulfill all these requirements, and should result in very compatible bioisosteres, i. e., have similar biological properties.

A review of certain antimalarials tested previously (10, 11, 5) suggests an analogy. Substituted phenanthrenemethanols have shown good antimalarial activity (although less so than the 4-quinolinemethanols) and no phototoxicity. When nitrogen was introduced into the ring system the antimalarial activity of the resulting azaphenanthrenes was less than the activity of its phenanthrene analog. By analogy, replacement of the quinoline nucleus with the naphthalene nucleus might result in compounds that were at least as active and not phototoxic. A number of 1- and 2-naphthalenemethanols have been prepared and tested (11), and showed modest activity. However, none had any substitution in the position analgous to the 2 position in the quinoline ring.




a




b

Figure 1

## Synthetic Background and Approach

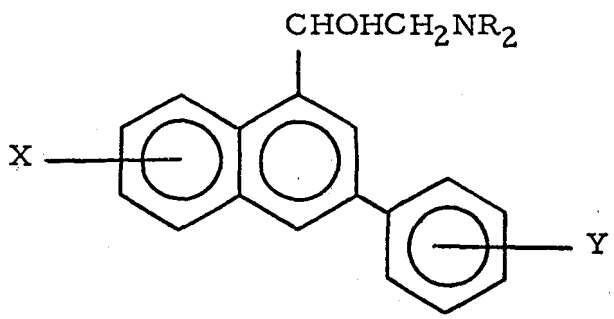
The target α-dialkylaminomethyl-3-phenyl-1-naphthalene-methanols are shown in Figure 2. It was desirable that the synthetic pathway be short and have possible commercial utility.

## Side Chain Preparation

Three basic methods exist for the preparation of the dialkylamino-methylmethanol side chain, and are shown as Routes A, B, and C.

Route A shows the methods generally used to prepare the side chain on the quinolinemethanols and naphthalenemethanols. Two paths were taken from the original aromatic acid, 16, (easily prepared in the quinolines) to the haloketone, 17. Lutz et al. (7) used both methods. The acid, 16, was treated with thionyl chloride to form the acid chloride, 17. The acid chloride was allowed to react with diazomethane to form a diazomethyl ketone, which, upon treatment with HBr or HCl, forms the halomethyl ketone, 19. The preparation of the methyl ketone, 18, is another means of obtaining 19 from 16. The methyl ketone was prepared

Figure 2




Compound No.

7 X = H:Y=4'-Cl; R=$C_2H_5$

8 R=$C_4H_9$

9 R=$C_7H_{15}$

10 X = 7-$OCH_3$; Y=4'-Cl; R=$C_2H_5$

11 R=$C_4H_9$

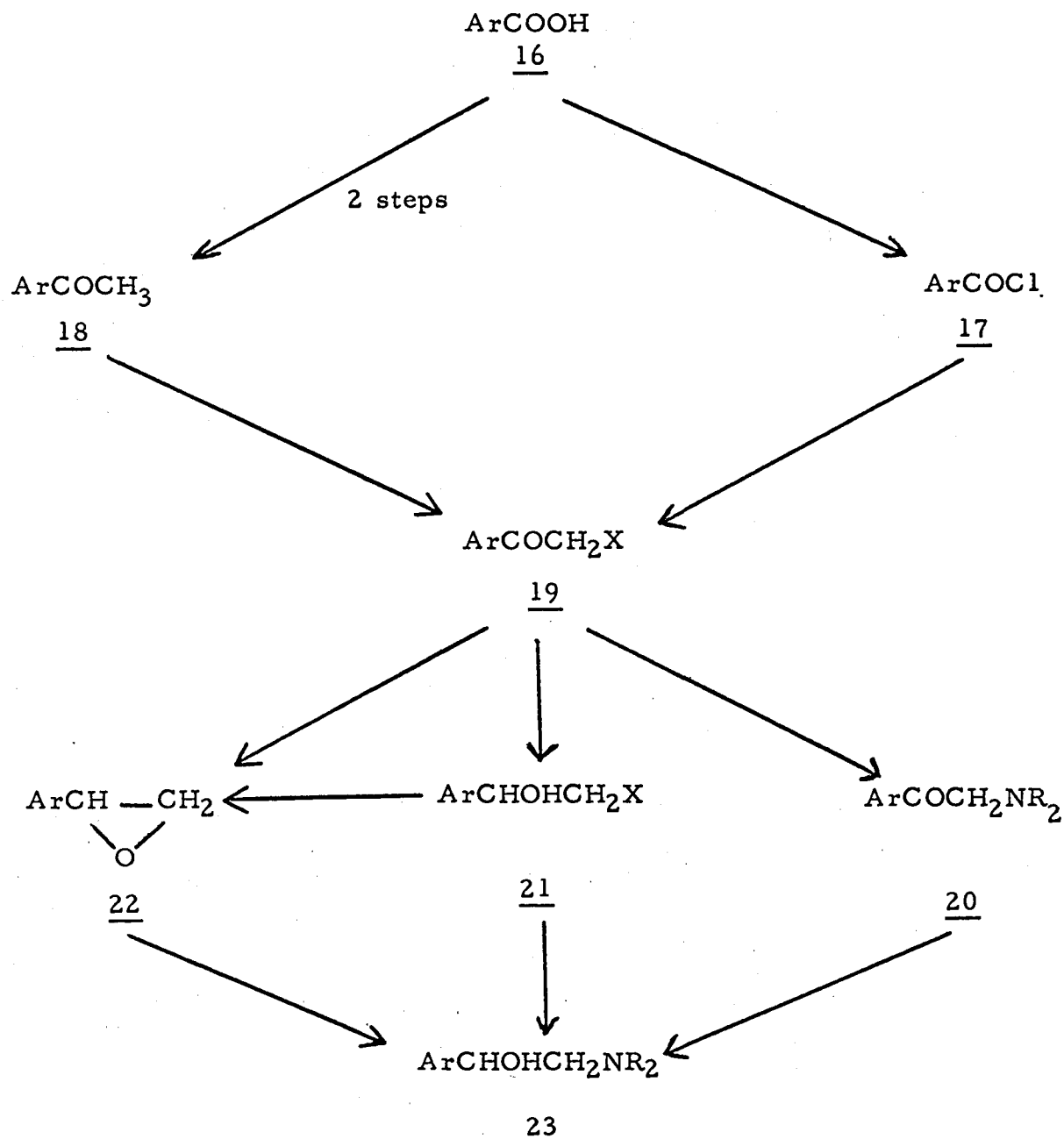
12 R=$C_7H_{15}$

13 X = 7-Cl; Y=3',4'-diCl; R=$C_2H_5$

14 R=$C_4H_9$

15 R=$C_7H_{15}$

Route A

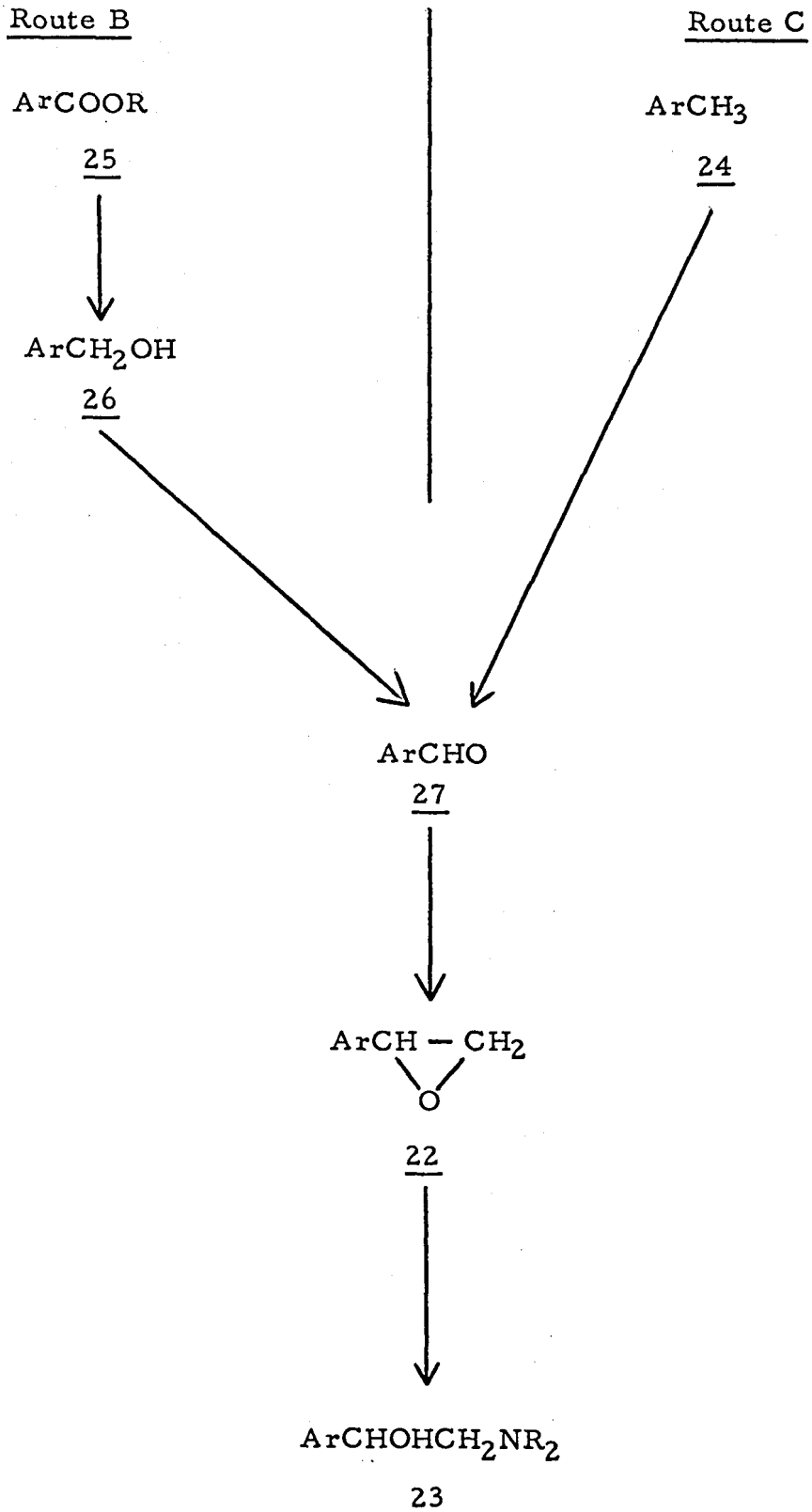



X = Halogen

Ar = Aromatic Nucleus

by refluxing the acid ester in dry benzene with sodium methoxide, and ethyl actetate, then hydrolyzing the resulting ketoester with sulfuric acid. Then the ketone was brominated. May and Mosettig (21) allowed the haloketone, 19, to react with the dialkylamine in ether at room temperature, and formed the dialkylaminomethyl ketone, 20. They prepared the dialkylaminomethyl methanol, 23, by allowing compound 20 to react with platinum oxide in methanol. The aminoketones, 20, are often undesirable because of their instability (22). Normally, cleaner products and better yields were obtained by the reduction of the halomethyl ketone, 19, with aluminum isopropoxide (7, 23). This formed the halohydrin, 21. The halohydrin was allowed to react with the appropriate dialklamine to produce compound 23. Winstein et al. (24) were able to prepare the dialkylaminomethyl methanol, 23, by allowing the haloketone, 19, to react with aqueous base forming the epoxide, 22. In this particular case the aromatic moiety was the naphthalene ring. More recently Atkinson and Puttick (25) went directly to the epoxide, 22, by reduction of the haloketone, 19, with sodium borohydride in ethanol.

Routes B and C represent more recent work. As is shown in Route B, it is possible to prepare the dialkylaminomethyl methanol, 23, from the acid ester, 25, in four steps (15). Reduction of compound 25 with lithium aluminum hydride produces the aryl methanol, 26. Oxidation of compound 26 by pyridine-$SO_3$ in DMSO produced the aromatic aldehyde, 27, according to the method of Parikh and Doering (26).


Route B
ArCOOR
25
ArCH2OH
26
Route C
ArCH3
24
ArCHO
27
ArCH — CH2
O
22
ArCHOHCH2NR2
23

The epoxide, 22, was prepared by allowing the aldehyde, 27, to react with a stoichiometric quantity of dimethyl sulfonium methylide (27).

Route C is the shortest of the three. In the case of the 8-quinolinemethanols, the dialkylaminomethyl methanol, 23, was prepared in 3 steps from the methyl substituted aromatic compound, 24. The methyl compound, 24, was oxidized to the aldehyde, 27, with selenium dioxide (28). Preparation of the epoxide, 22, and the final compound, 23, was as in Route B.

Route C is the method of choice. It is the shortest, and it involves relatively simple reactions and intermediates.

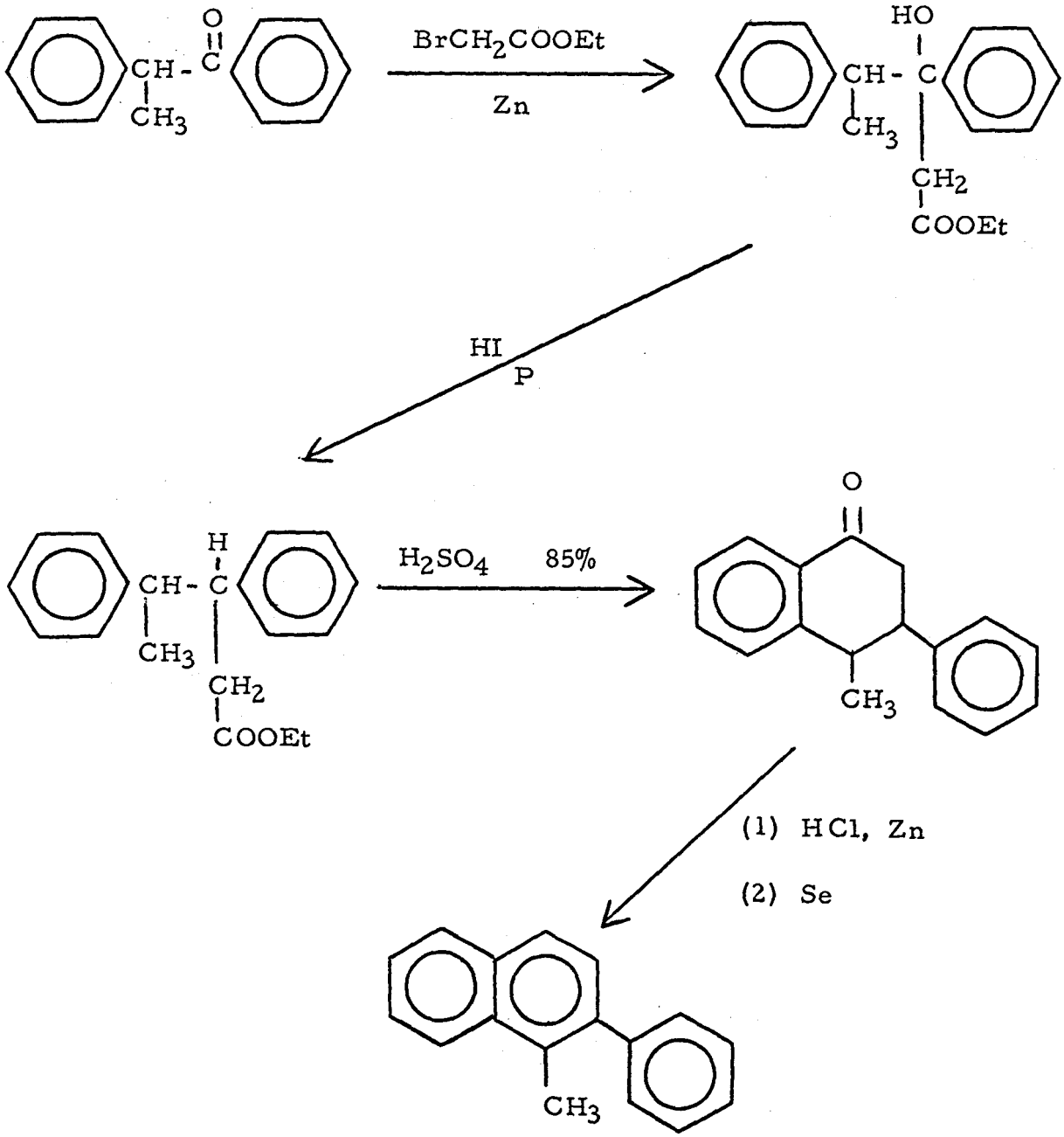
## Preparation of the Ring

Preparation of substituted 1-methyl-3-phenylnaphthalenes is now required to make the proper aromatic starting material for Route C.

T. Zincke and A. Breuer (29) described what was possibly the first case of aromatic cyclodehydrogenation. The compound 2-phenylnaphthalene was prepared by boiling phenylglycol or phenylacetaldehyde in 50% sulfuric acid. K. von Auwers (30) prepared 2-methyl-6-(4-methylphenyl)-naphthalene by the hydrolysis of p-methyl ($\beta,\beta$-dichlorethyl) benzene. These and similar methods have the disadvantage of not producing a single methyl substitution at the 1 position.

Spring (31) prepared 1-methyl-2-phenylnaphthalene by the method shown in Route D. No yields were reported. The first and only report

Route D


BrCH2COOEt
Zn
HO
CH-C
CH3
CH2
COOEt
HI
P
H
CH-C
CH3
CH2
COOEt
H2SO4
85%
O
CH3
(1) HCl, Zn
(2) Se
CH3

of a synthesis of 1-methyl-3-phenylnaphthalene was by Quillet and Dreux in 1966 (32). Their route is shown in Route E. They reported poor overall yields. Further, they obtained a mixture of 1-methyl-3-phenylnaphthalene, 1-methyl-3-phenyl-1, 2, 3, 4-tetrahydronaphthalene, and 4 unidentified secondary compounds comprising 12% of the product.

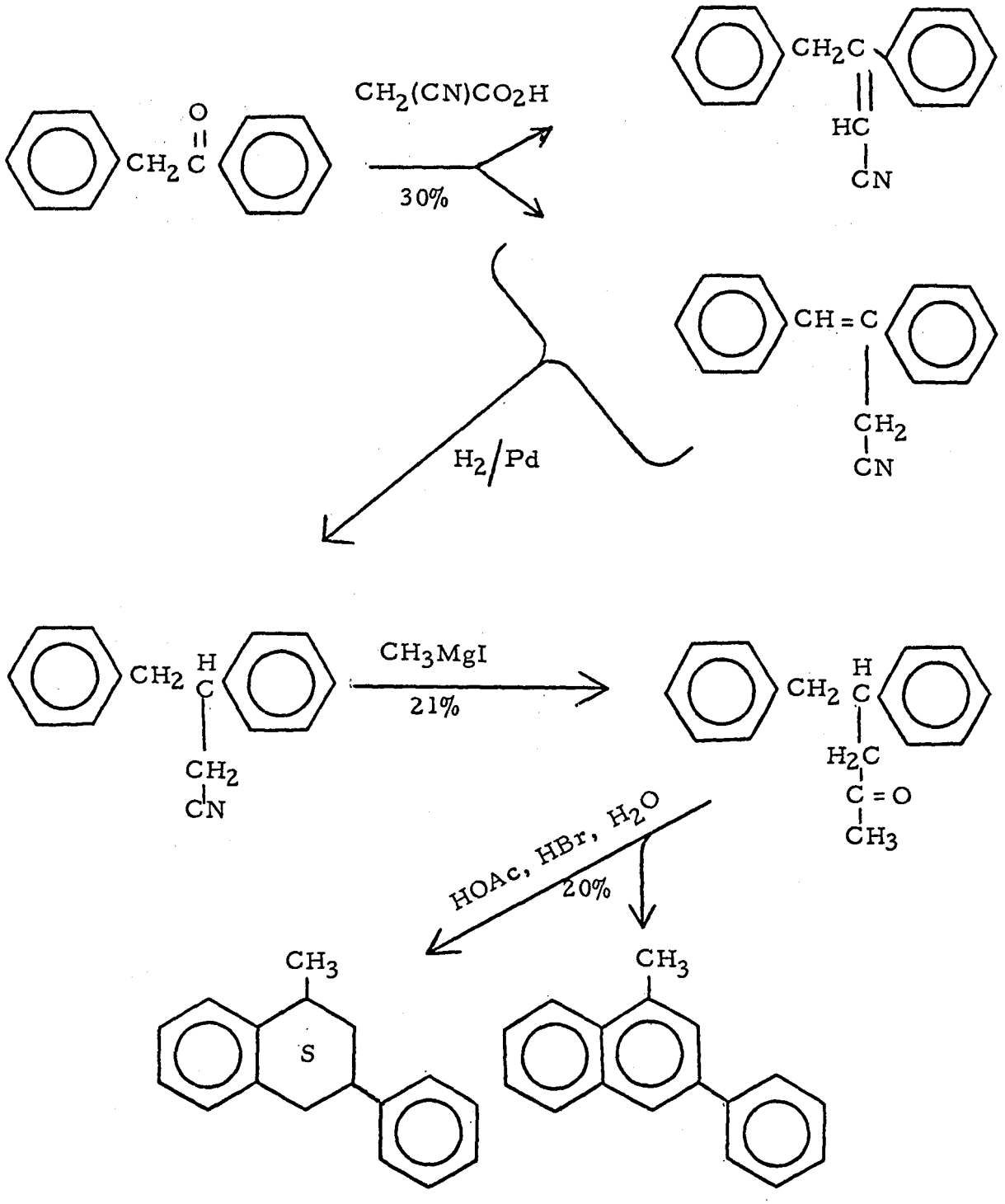
Quillet and Dreux's method for the preparation of 1-methyl-3-phenylnaphthalenes appears tedious and suffers from poor yields. Two new routes, Routes F and G, were devised. The 4-chlorophenyl moiety is used as an example.

Route F produces the substituted 1-methyl-3-phenylnaphthalene in essentially three steps. Two advantages of this route are its use of simple starting materials and the simple reactions involved.

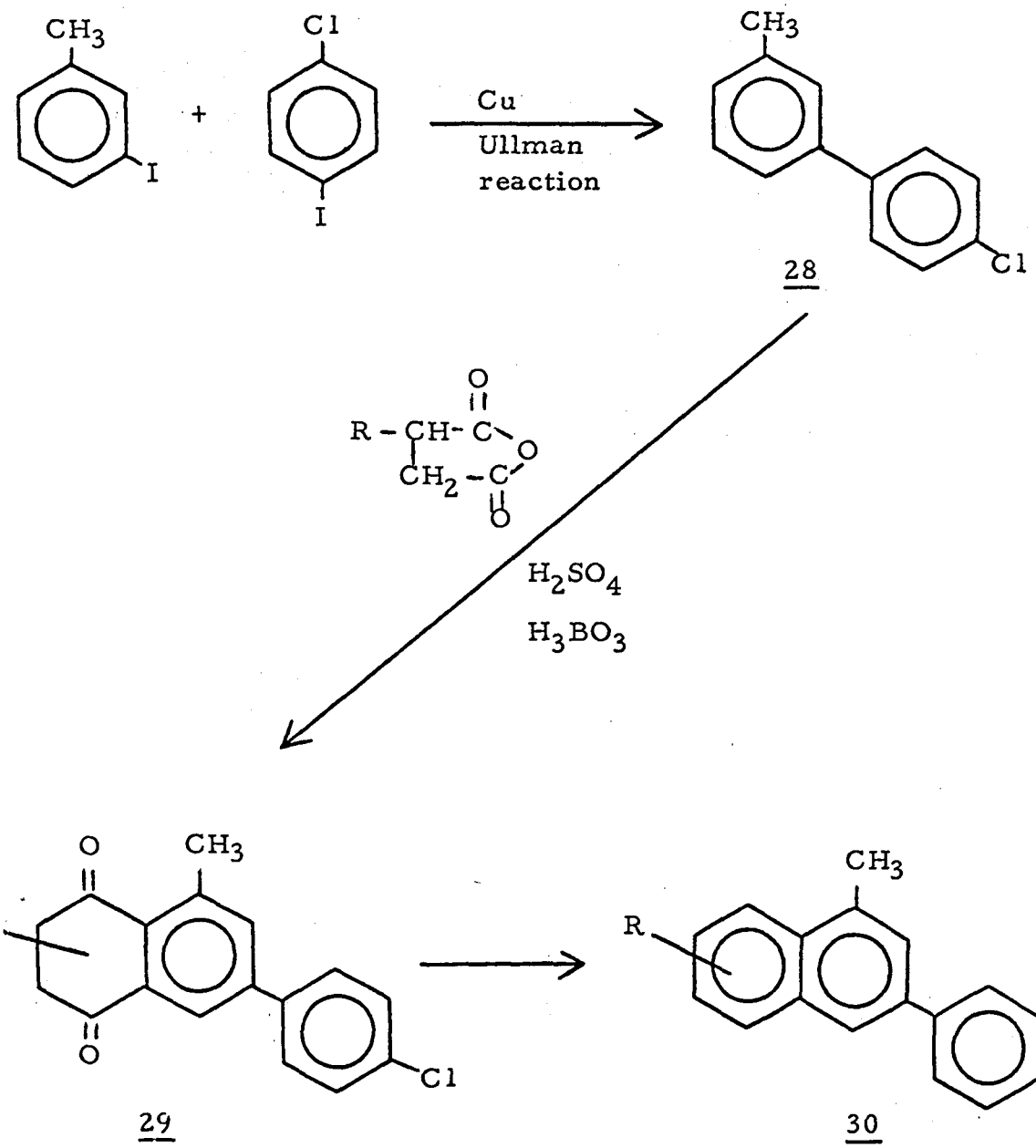
The Ullmann reaction is widely used for the condensation of an arylhalide (33). It is usually unsuitable for mixed condensations because of the large number of side reactions possible, and the variable yields. However, Gore and Hughes (34) reported a quantitative Ullmann reaction in the preparation of 2,2'-dinitrodiphenyl from o-iodonitrobenzene using a freshly precipitated copper catalyst. Therefore, if a quantitative reaction were possible in this case, the yield of the desired compound might be acceptable.

A modification of the Haworth synthesis (35) yields the diketo compound, 29, from the diphenyl, 28. The Haworth synthesis is a general method of obtaining various naphthalenes from substituted benzenes

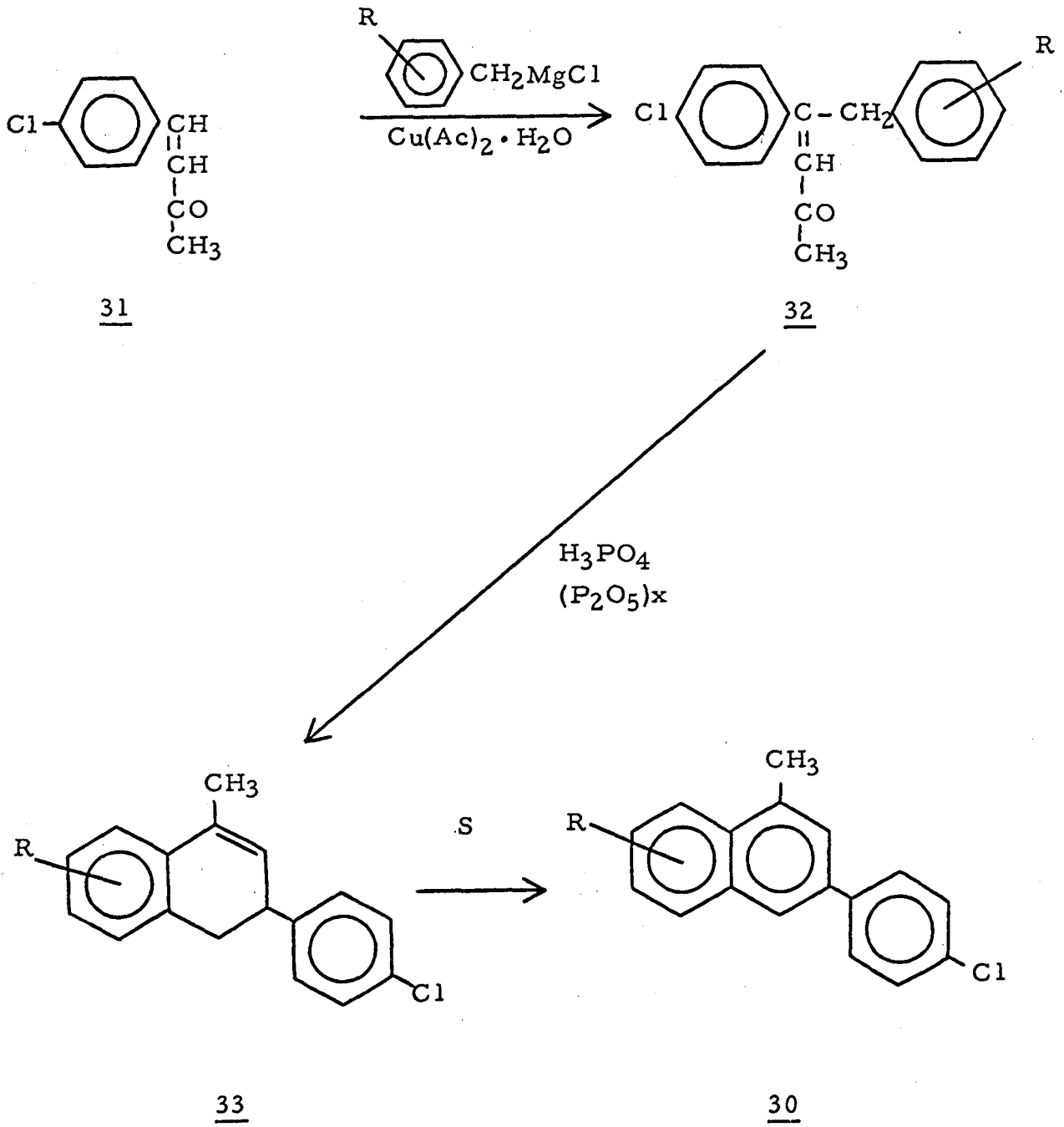
Route E


CH2(CN)CO2H
30%
CH2C
HC
CN
CH=C
CH2
CN
H2/Pd
CH2
H
C
CH2
CN
CH3MgI
21%
CH2
H
C
H2C
C=O
CH3
HOAc, HBr, H2O
20%
CH3
S
CH3

Route F


CH3
I
+
Cl
I
Cu
Ullman
reaction
CH3
Cl
28
R - CH - C
O
CH2 - C
O
O
O
H2SO4
H3BO3
O
CH3
R
O
Cl
29
CH3
R
Cl
30

Route G


R
CH2MgCl
Cu(Ac)2 • H2O
Cl
CH
CH
CO
CH3
C - CH2
R
31
32
H3PO4
(P2O5)x
CH3
R
S
Cl
33
30

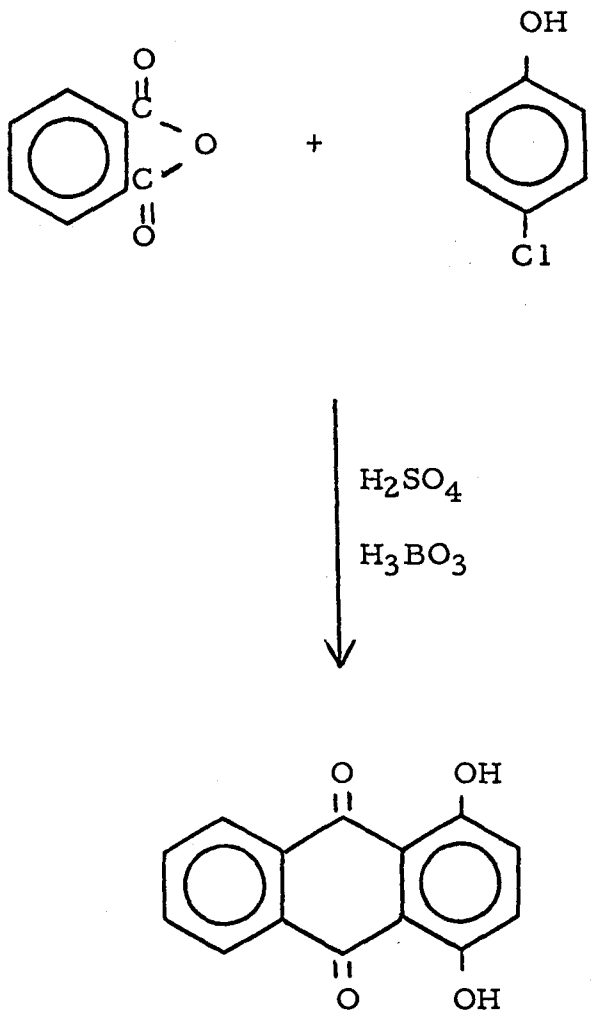
and succinic anhydrides. It was considered necessary to perform a Clemmensen reduction of the keto group, formed from the first condensation with the ring, before condensation of the remaining carboxyl group would occur with the ring. But Bigelow and Reynolds (36) prepared Quinizarin as shown in Route H. In the present case, if the methyl function imparted enough activity to the attached phenyl ring, then a substituted succinic anhydride could condense with the ring by Bigelow's method. The ring with the chlorine attached should be less active. Also, the site for attachment could be ortho to both the methyl and 4-chlorophenyl groups, however, the bulkier 4-chlorophenyl group should offer steric hindrance to the condensation. Therefore, substitution should occur ortho to the methyl group.

The diketone, 29, would then be converted to the substituted naphthalene, 30, by reduction with Zn and HCl, and dehydrogenation with selenium or sulfur.

Route G produces the substituted 1-methyl-3-phenylnaphthalene in the same number of steps as Route F. Usually the benzalacetone would have to be prepared. Drake and Allen (37) reported a facile preparation of benzalacetone from benzaldehyde and acetone. A large excess of acetone was used to lessen the formation of dibenzalacetone and other condensation products. Extrapolation of this to 4-chlorobenzalacetone, for example, would be fairly simple.

The diphenyl pentanone, 32, is the result of 1,4 addition of

Route H



benzylmagnesium chloride to compound 31 by the method of Marshall et al. (38). They prepared cis-9,10-dimethyl-2-decalone by the reaction of methylmagnesium iodide with 10-methyl-1(9)-octal-2-one, using cupric acetate as a catalyst. The use of copper salts to promote, 1,4 addition was noted by Kharasch and Tawney (39). Birch and Smith (40) discovered that cupric acetate in tetrahydrofuran, instead of the usual cupric chloride, gave increased yields of 1,4 addition to their ketones. Munch-Petersen and Anderson (41) found that the 1,4 addition of Grignard reagents to $\alpha,\beta$ unsaturated esters gave better yields at low temperatures. Kharasch and Reinmuth (42) also noted better yields at lower temperatures.

The pentanone, 32, is mixed with polyphosphoric acid and heated to promote cyclization. Fieser and Fieser (43) cite the numerous advantages of polyphosphoric acid over other cyclization agents, such as sulfuric acid. For instance, polyphosphoric acid is not an oxidizing agent, and it is less prone to cause rearrangements. The actual cyclization product might be a mixture of the tetrahydronaphthalene and the totally aromatic naphthalene, rather than the dihydronaphthalene, 33, (32).

The cyclization product, whether a mixture of the tetrahydronaphthalene and naphthalene, or the single product, dihydronaphthalene, should be aromatized by oxidation with sulfur (44) to form the substituted 1-methyl-3-phenylnaphthalene, 30.

# DISCUSSION

The attempted preparation of 4-chloro-3'-methyldiphenyl, 28.

Three attempts were made to prepare 4-chloro-3'-methyldiphenyl. In the first attempt, m-iodotoluene and p-bromochlorobenzene were added in equimolar amounts with a commercial grade of copper powder to dimethylformamide, and were refluxed. Workup of the reaction mixture resulted in the recovery of the starting material. In the second attempt, the components were mixed without solvent and heated to 200° with an activated copper catalyst prepared by the method of Gore and Hughes (34). Isolation resulted in the recovery of the starting material. The third attempt was as the second except the reaction mixture was heated to reflux for 6 hr. Isolation and vacuum distillation indicated a complex mixture. A sample of the product was analyzed by mass spectra. The composition of the product proved to be a little 4-chloro-3'-methyldiphenyl, considerable 4,4'-dichlorodiphenyl, some 4-chloroiodobenzene, and some 4-bromoiodobenzene. It now appeared that the mixed Ullmann reaction was going to give poor yields at best. Thus, the complete synthetic route, which started with this reaction, was abandoned.

4-Chlorobenzalacetone, 31.

Preparation of the benzalacetone went fairly well, except for variable yields, ranging from 20 to 77%. After numerous runs, it

appeared that a number of conditions had to be met to achieve good yields. First, the size of the run had to be no larger than 1.0-1.5 mol. It was necessary to keep the reaction mixture below 15-20°. Otherwise, considerable darkening of the solution and polymerization resulted, reducing the yield. The reaction appeared to have an induction period. At first, addition of the aqueous base had no effect upon temperature, and the solution remained colorless. After one-third of the base had been added, the solution would suddenly turn yellow, and the temperature would rise rapidly. It was difficult to keep the temperature below 20° during this period. The larger the preparation, the more difficult the temperature was to control with subsequent reduction of yields. Therefore, the optimum size of the run was 1.0-1.5 mol.

Second, during removal of solvents it was best to keep the temperature of the solutions low. Excess heating darkened the residues and lowered the yield.

Third, less decomposition of the benzalacetone was obtained if the pot mixture was rapidly stirred while distilling under vacuum. Use of boiling chips or capillary bleed materially lowered the yield. Also, an oil bath was better than a heating mantle.

4-(4-Chlorophenyl)-5-phenyl-2-pentanone, 36.

The most remarkable aspect of the considerable amount of study of the preparation of this compound was the consistently poor yield. The

most difficult problem of the preparations was the inability to isolate pure products except by the most inefficient means. Further complicating the work was the initial lack of a gas chromatograph to analyze the complex mixtures produced in the preparations. Once this tool became available, more intelligent assessments of the products were possible.

Preparation of the Grignard reagent was initially carried out by a standard technique of adding the benzyl bromide in an equal volume of ether to a slight molar excess of magnesium covered by ether. A nitrogen atmosphere was used to protect the Grignard reagent. Rate of addition was governed by the reflux rate. A considerable amount of coupling or "Wurtz" product resulted from this preparative technique. Kharasch (45) noted that the reactivity of organic halides in Grignard reactions was in the order RI > RBr > RCl, R being the same throughout. The higher the reactivity of the halide the greater its chance of engaging in side reactions, e.g. formation of the Wurtz product. Kharasch (46) also noted that dilute solutions gave better yields of Grignard reagent. The optimum concentration was a $Et_2O$/RX ratio of 10/1 in the case of benzyl chloride. Thus, in later preparations of the Grignard reagent, benzyl chloride was used instead of benzyl bromide, and $Et_2O$/RX ratios were on the order of 10/1, and even 15/1. These changes reduced the amount of coupling product, but seemed to have

little effect on the purified yield of 1,4 addition product.[1]

Dry[2] tetrahydrofuran solutions of 4-chlorobenzalacetone and cupric acetate monohydrate were always added to the Grignard reagent. Inverse addition was never attempted. Munch-Petersen and Anderson (41) obtained significantly less 1,4 product when inverse addition was attempted. They also noted that, in general, portionwise addition of the copper salt was preferable to bulk addition. Concentrations of the 4-chlorobenzalacetone and the cupric acetate were not varied. They were necessarily dilute because of the limited solubility of the copper salt in tetrahydrofuran.[3] The reaction was exothermic, and required constant monitoring of the addition rate to keep the temperature of the

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1. This statement does not imply that the amount of 1,4 addition product was not increased in the reaction. Gas chromatographic analysis showed that there was more 1,4 product as well as 1,2 product. But subsequent losses in purification offset the modest increase in crude yield.

2. The tetrahydrofuran was dried by distilling from a suspension of $LiAlH_4$ in THF.

3. S. P. Acharya of this laboratory noted that cuprous halides were insoluble in THF and ether. This might account for Birch and Smith's (40) better yield with the cupric acetate salt.

reaction mixture within limits. One experiment was attempted without the presence of the copper salt and THF. The 1,4 addition did occur but the yield of product was halved. Kharasch (47) suggested the use of an organozinc reagent to suppress 1,2 addition. One study was made by preparing the Grignard reagent then adding anhydrous zinc chloride to form the organozinc reagent. Only starting material was recovered.

The temperature of the reactions was -20°. Experiments at 0° and -35° did not affect the yields. One hour of refluxing was added routinely. However, in one experiment, the omission of this step had no conclusive effect on the yield of 1,4 product.

The total time of a run was normally 20 hr from start of addition.[1]

Decomposition of the reaction mixture with saturated aqueous $NH_4Cl$ solution was routine. This resulted in a purple water insoluble mass. If air was bubbled through the mass, or the whole flask and contents were shaken in the presence of air, the mass would turn blue and become water soluble. The change was probably due to the oxidation of cuprous ion to cupric. One problem with this method was the formation of emulsions with the ether layer. Often the emulsions could be

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1. One experiment of 2 - 3 hr duration was attempted by S. P. Acharya of this laboratory. Almost all of the starting material was recovered.

broken only by acidification with dilute HCl. In later experiments the ether layer was decanted from the purple mass without any effect on the yield. The ether layer was extracted with $Na_2S_2O_3$ solution to remove any residual cuprous ion.

Purification of the reaction product was a major task. Initially, gas chromatographic analysis of the mixture showed five poorly defined major peaks.[1,2] By distilling the product through a 200 mm Vigreaux column, a rough separation could be made. Subsequent analysis always showed the complete elimination of one peak. However, the purest product obtained by this method always showed the 1,4 product contaminated by the three other impurities. Numerous efforts were made to crystallize the crude product. Methyl alcohol and benzene were the most successful crystallizing solvents. When crystallization of the reaction mixture from methyl alcohol or benzene was the method used the yields were less than half that of the distilled product. However, much purer 1,4

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1. A number of experiments were run before a gas chromatograph was used for analysis. The complexity of the reaction product was not obvious until the instrument was available. Much time was wasted trying to purify and use grossly impure products.

2. Actually, more than five peaks were recorded. But the other peaks were small, indicating smaller amounts of these compounds. Also, they were readily removed in any of the purification steps.

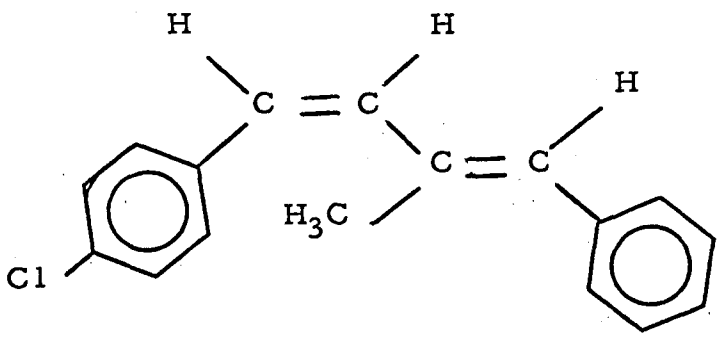
addition product resulted. The method used with greatest success on large runs was trituration of a partially distilled sample with cool methyl alcohol and benzene. The three impurities themselves were never separated completely. Gas chromatographic analysis of the trituration steps showed that the two solvents were each partially selective in removing one of the three impurities. A sample was recovered that showed only two compounds in a 9/1 ratio. Mass spectral analysis of the two showed only one parent peak and no indication of a mixture. This suggested that the mixture was really two isomers. An nmr anaylsis lent further proof. It appeared that the three impurities were isomers of 1-(4-chlorophenyl)-3-methyl-4-phenyl-1,3-butadiene. The most likely structures are 37, 38, and 39. The fourth peak, which disappeared upon distillation, was thought to be some of the initial alcohol product that dehydrated to a 1,2 isomer.

The method described in the experimental section produced the largest yield of pure product.

Cyclization of 4-(4-chlorophenyl)-5-phenyl-2-pentanone

The most facile method for cyclization of the pentanone in polyphosphoric acid is shown in the experimental section.

The initial preparations were not successful for two reasons. First, impure starting material produced mixtures of such complex nature that purification was impossible. Second, the true nature of the

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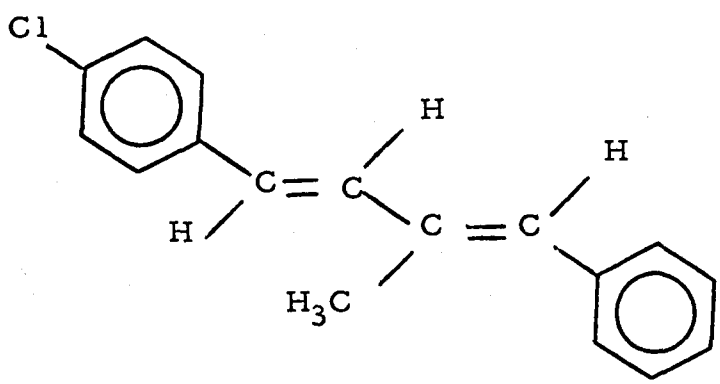


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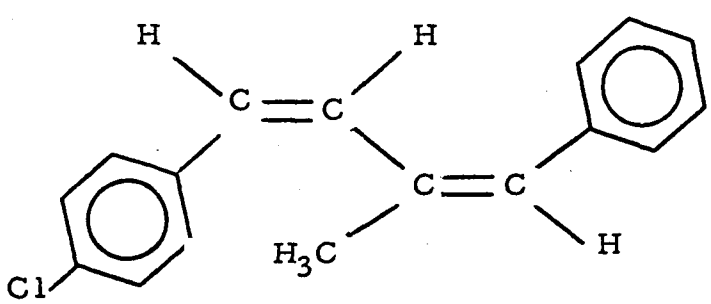


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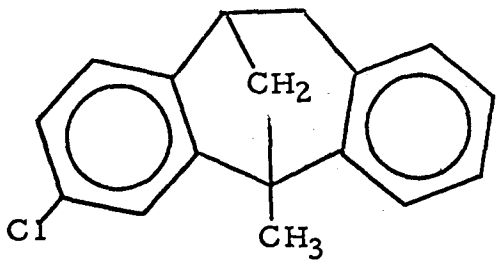
major products was not immediately known.

At first, the flask containing the pentanone and polyphosphoric acid was placed in a bath that was being heated to 200°. After reaching 200° heating was continued until ir analysis showed no carbonyl band. The mixture was removed from the bath and the organic residue was recovered. Both crystallization and vacuum distillation were fruitless for purification of the product. The nmr spectra of the best sample was unaccountably complex in the 6.5-9.0$\tau$ region, as well as the 2-3$\tau$ region. The assumption made at this time was that the sample consisted of three major compounds; 3-(4-chlorophenyl)-1-methyl-1,2,3,4-tetrahydronaphthalene, 3-(4-chlorophenyl)-1-methyl-3,4-dihydronaphthalene, and 3-(4-chlorophenyl)-1-methylnaphthalene. This mixture would be expected to dehydrogenate to a pure product of the fully aromatic naphthalene. Continued failures to recover pure products in the dehydrogenation step indicated that something was amiss. Analysis by gas chromatograph showed that three major products were present. But, during the dehydrogenation attempt, analysis showed one peak became larger, one almost disappeared, and one showed no change. Therefore, one of the peaks was not one of the naphthalene derivatives mentioned previously. At this point the cyclization procedure, by chance, was altered slightly due to a change in the type of heating bath. The heating bath was preheated to 200°. The flask and contents were plunged into the bath and the reaction was completed as before. Analysis by gas chromatography showed that

these conditions resulted in a product consisting of 40% of the unknown material. Cooling of the reaction mixture caused the normally liquid product to solidify, and crystals separated. Purification resulted in the isolation of a pure sample of the unknown compound. Subsequent nmr and ms analysis showed the product to be 5,10-methano-7-chloro-5-methyl-dibenzo (a,d) cycloheptane, 40, (RRI 4806). A purified sample was sent for elemental analysis. The reported values confirmed the correct empirical formula, $C_{17}H_{15}Cl$. Further study revealed that the amount of this unwanted product could be held to 15% or less during cyclization by immersing the flask and contents in a cold bath. The bath was raised to 200° over a 2 hr period, and the reaction completed as before. Purification of the mixture was left until the next step.

3-(4-Chlorophenyl)-1-methylnaphthalene, 41.

A facile preparation of 3-(4-chlorophenyl)-1-methylnaphthalene is recorded in the experimental section. The first attempts to oxidize the mixtures from the cyclization reactions resulted in intractable products. Some of the problems encountered with this reaction have been discussed in the preceding section on cyclization. It should be mentioned that presence of the 1,2 product in the starting materials for cyclization may have resulted in the formation of 1-(4-chlorophenyl)-

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3-methylnaphthalene as an unwanted by product.[1] This, of course, would seriously contaminate the oxidation step. Reaction of the purer mixtures with sulfur went smoothly. The course of the reaction was followed by injecting samples into the gas chromatograph and observing the disappearance of the peak corresponding to the tetrahydronaphthalene. After the reaction was completed the ether solution of the reaction product was stirred with mercury for a number of hours to insure the complete removal of sulfur. If this was not done considerable sulfur contamination of the distillates resulted during vacuum distillation. The methanocycloheptane impurity was best removed by sublimation in a device which stirred the residue very rapidly while maintaining a pressure of 0.05-0.02 mm. When the residue was heated to 135° the amount of the methanocycloheptane in the residue dropped to less than 1% in less than 2 hr. The sublimed methanocycloheptane could be recovered from the neck of the flask. The apparatus which was best suited for this method was a spinning band column. Although no product distilled, the column incorporated a rapid stirrer (1700 rpm) and could sustain the necessary vacuum. Other methods were tediously slow.[2] This sample

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1. S. P. Acharya, in a preparation of 7-chloro-3-(4-chlorophenyl)-1-methylnaphthalene, was able to isolate 7-chloro-1-(4-chlorophenyl)-3-methylnaphthalene. He previously had been unable to adequately separate the 1,2 and 1,4 addition products.

2. Stirring the contents of the flask with a magnetic stirrer would not lower the amount of methanocycloheptane product below 10%, even after 3 days. A rotoevaporator proved somewhat more efficient, yielding a sample with 3-5% methanocycloheptane product after two days.

was removed from the apparatus and was distilled in a short path distillation apparatus to recover the purified 3-(4-chlorophenyl)-1-methylnaphthalene.

One attempt was made to dehydrogenate the ring by the method of Melton et al. (48). The crude cyclization mixture and 10% Pd/C were heated neat at 300° for 1 hr. Analysis by ir, nmr, and mass spectra indicated that the starting materials had been dechlorinated.

3-(4-Chlorophenyl)-1-naphthaldehyde, 42.

A facile preparation of the aldehyde is given in the experimental section. At first, a mixture of 3-(4-chlorophenyl)-1-methylnaphthalene and $SeO_2$ was heated and the resulting mixture worked up. Intractable residues were obtained. Then a triglyme solution of the aromatic compound, 41, and the stoichiometric quantity of $SeO_2$ was refluxed, and the resulting suspension was worked up. The yield of aldehyde was less than 40%. Next a mixture of triglyme and water was used as a solvent system. The $SeO_2$ was insoluble in the triglyme but was soluble in the triglyme-$H_2O$ mixture. The mixture was refluxed. Analysis by gas chromatography indicated little reaction was occuring. Only after the $H_2O$ was allowed to boil off did any significant reaction occur. However, the yield of the naphthaldehyde was low. Finally, a stoichiometric quantity of $SeO_2$ was added to a refluxing solution of the aromatic compound in triglyme. Analysis by gas chromatography showed only 50% reaction. Further

additions of excess $SeO_2$ in $H_2O$ raised the yields to 93%. The excess $SeO_2$ seemed to offer no difficulty during the purification of the aldehyde. Raney nickel was used to remove any residual selenium not removed by previous filtration. Elemental and ir analysis confirmed the structure.

3-(4-Chlorophenyl)-1-(1,2-epoxyethyl)-naphthalene, 43.

The epoxy compound was prepared by the addition of a THF-DMSO solution of freshly prepared dimethylsulfonium methylide to the aldehyde in THF. The methylide was prepared at low temperatures because of its instability. However, the reaction with the aldehyde was at room temperature. Stoichiometric amounts of the methylide were used, rather than an excess, because work with other compounds (15) indicated better yields of the epoxy compounds were obtained. Purification of the epoxy compounds often resulted in decomposition, Therefore, the recovered products were used without purification, and usually gave satisfactory results.

3-(4-Chlorophenyl)-$\alpha$-dialkylaminomethyl-1-naphthalenemethanol hydrochlorides, 7, 8, and 9.

The preparations of these compounds are grouped together in this section. The individual preparations are included in the experimental section.

Generally, the epoxyethyl naphthalene, 42, was heated with an excess of the dialkylamine under nitrogen atmosphere. The preparations of the dibutylamine and diheptylamine derivatives were carried out at 160° and 170° respectively. It was felt that the reflux temperature of diethylamine (56°) would not be high enough to bring about a reaction between the amine and the epoxide. Thus, the reaction mixture was placed in a stainless steel bomb and was heated to 120° for 4 days.

Isolation of the products was similar in all cases. The unreacted dialkylamines were removed by heating the reaction mixture under vacuum and distilling the amine. Dibutylamine and diethylamine were easily removed on a rotoevaporator while heating in a boiling water bath. Evacuation by a water aspirator was sufficient. The diheptylamine required more severe conditions. This amine was distilled at 150° and 0.1 mm pressure, and required an oil bath and mechanical pump.

The residues were dissolved in ether and the products were precipitated with ethereal HCl. Usually, a small amount of the dialkylamine hydrochloride was removed first. Composition and purity of the fractions were monitored by a check of the melting point. The fractions containing the purest compound were combined and were crystallized from chloroform-acetone or acetone. Ethanol, a common solvent for crystallization of similar quinoline compounds, was not suitable because the naphthalenemethanols were too soluble. Elemental and ir analysis confirmed the structures.

3-(4-Chlorophenyl)-7-methoxy-1-naphthaldehyde, 44.

This compound was prepared by the reaction of 3-(4-chlorophenyl)-7-methoxy-1-methylnaphthalene[1] with $SeO_2$, as described in the experimental section. Excess $SeO_2$ was necessary to achieve the maximum yield of aldehyde, as was the case with 3-(4-chlorophenyl)-1-naphthaldehyde. Analysis of the reaction mixture by gas chromatography indicated a maximum conversion of 85%. Attempts were made to crystallize the residue from a number of solvents. Eventually two products were recovered. One product crystallized from benzene. Elemental and nmr analysis showed this to be the desired aldehyde. The second product was recovered by evaporating the benzene mother liquor. The compound had no distinct melting point. Nmr analysis (difficult because of limited solubility of the compound in deuterated solvents) showed the absence of any aldehydic proton. The compound was not characterized further.

3-(4-Chlorophenyl)-1-(1,2-epoxyethyl)-7-methoxy-naphthalene, 45.

The preparation of this compound is described in the experimental section, and is similar in all respects to that of 3-(4-chlorophenyl)-1-(1,2-epoxyethyl)-naphthalene. As was the usual practice, the product was carried to the next synthetic step without purification.

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1. The sample of 3-(4-chlorophenyl)-7-methoxy-1-methylnapthalene was already available from a previous preparation by S. P. Acharya of this laboratory.

3-(4-Chlorophenyl)-α-dibutylaminomethyl-7-methoxy-naphthalene-methanol hydrochloride, 11.

The preparation of this compound is described in the experimental section. The procedure was the same used to prepare 3-(4-chlorophenyl)-α-dibutylaminomethyl-1-naphthalenemethanol hydrochloride.

3,4-Dichlorobenzalacetone, 46.

The preparation of this compound is described in the experimental section, and was similar to the preparation of 4-chlorobenzalacetone, 35, An effort was made to monitor the reaction by gas chromatography. After 3 hr the reaction showed a 50-50 mixture of the starting material, 35, and the product, 46. The reaction was allowed to continue. Analysis of the recovered solid showed a 60/40 mixture. However, there appeared to be a large amount of material the gas chromatograph was not showing. Purification was similar to that of compound 35. The structure was confirmed by nmr analysis.

An attempt to prepare and cyclize 4-(3,4-dichlorophenyl)-5-(4-chlorophenyl)-2-pentanone.

The preparative procedure was similar to that for 4-(4-chlorophenyl)-5-phenyl-2-pentanone. The only significant change was the cooling of the reaction mixture to -55° instead of -20°. Analysis of the product by gas chromatography showed a large "mound" of superimposed peaks. Although there appeared to be a dominant compound, it was not clear whether it was the 1,4 addition product, or something else. Ir showed a large carbonyl band compared with the other bands. Previous experience had shown this type of mixture almost impossible to purify. (See note 1 in the discussion of the preparation of 3-(4-chlorophenyl)-1-naphthalene.) It was decided to attempt a reaction with polyphosphoric acid.

The mixture was treated with polyphosphoric acid as previously described for 3-(4-chlorophenyl)-1-methylnaphthalene. However, in this reaction, a diffuse carbonyl band (5.7-5.85$\mu$) remained, even after 15 hr of heating. Isolation of the product left a highly complex mixture. A number of solvents were tried in an attempt to crystallize the product. The mixture proved intractable. The mixture was vacuum distilled and what appeared to be a major product was recovered. Gas chromatographic analysis of this product showed 8 major peaks (at least 3 superimposed) and numerous minor peaks. An analysis of the mixture with thin layer chromatography was undertaken to find a system

suitable for a column chromatographic separation of the components. Strips of silica gel and alumina, activated and unactivated, were tried with numerous solvent systems and mixtures. The only combination that appeared to give any separation at all was 30-60° petroleum ether and unactivated silica gel. All samples from the attempted separation showed multiple peaks by gas chromatographic analysis. The purest fraction consisted of a large peak composed of at least three components. No further purification was attempted.

## Biological Activity

Only one of the compounds has been screened for both antimalarial and phototoxic activity: 3-(4-chlorophenyl)-$\alpha$-dibutylaminomethyl-1-naphthalenemethanol hydrochloride. Results of these tests and a comparison with test results (49) of the quinolinemethanol analog, are summarized in Table 1[1]. Two facts are evident from the results. First, the naphthalenemethanol is free from phototoxic activity under the conditions tested (14). Second, and even more striking, is the remarkable activity of the naphthalenemethanol compared to the quinolinemethanol. Normally, no substitution in the second ring of these systems results in little antimalarial activity. Addition of a -Cl in the 7 position of the above quinolinemethanol increases the antimalarial activity of the quino-

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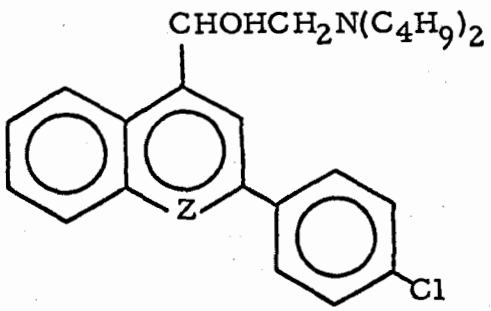
1. The tests were against Plasmodium berghei in mice (50).

Table 1




| | Change in Mean Survival Time[a] or No. Cures[b] Dosage (mg/kg) | | | | Phototoxicity Dosage (mg/kg) |
|---|---|---|---|---|---|
| Z | 20 | 40 | 80 | 160 | |
| =N- | 5.1 | 7.3 | 8.3 | 11.3 | Pos. @ 66 |
| =CH- | 2.5 | 8.3 | 5C | 5C | Neg. @ 400 |

(a) Mean Survival Time of treated mice - Mean Survival Time of controls.

(b) No. of treated mice in groups of 5 surviving to 30 days or more.

linemethanol to a curative level, at a dose of 40 mg/kg body weight, in mice. The activity of the naphthalenemethanol with no substitution in the second ring is especially interesting in light of the above facts. Also, the 7-chloro analog of the quinolinemethanol shows phototoxic activity, at a level of 5 mg/kg body weight, whereas the naphthalene-methanol is not phototoxic.

# EXPERIMENTAL

Instrumentation

Infrared spectra were obtained with a Perkin-Elmer Model 21 spectrophotometer.

Nuclear magnetic resonace spectra were obtained with a Varian Model A-60 nuclear magnetic resonance spectrometer.

Mass spectra were obtained with a Hitachi Model RMU-6H mass spectrometer.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus, and are uncorrected.

Gas chromatographic analyses were carried out on an F and M Model 810 gas chromatograph. Two columns were used: a 4 ft. silicone rubber 1/4" column; a 6 ft. 3% OV-225 on Variport-30 1/4" column.

4-Chlorobenzalacetone, 31.

A 1 liter 3 neck flask was equipped with a thermometer, dropping funnel, and mechanical stirrer. The flask was charged with 4-chlorobenzaldehyde (160 g, 1.14 mol) and reagent grade acetone (500 ml). The solution was cooled just below 10° in an ice bath. A solution of NaOH (2.5 g) in $H_2O$ (50 ml) was added slowly. Initially the temperature remained at or below 10°. After 1/3 of the basic solution had been added the temperature suddenly began to rise very rapidly. Even with efficient stirring and cooling in the ice bath, the temperature reached 18° before

control was established. Then the temperature was brought down below 10° and the addition was completed. The yellow solution was stirred at 10° for 2 hours. The ice bath was removed, and the solution was stirred for another 2 hours. Diluted HCl was added until the contents of the flask were acidic. At this point the solution turned pale yellow and separated into 2 layers. (The solution had turned brown during the course of the reaction). Both layers were transferred to a separatory funnel. The bottom organic layer was removed. The remaining aqueous layer was extracted twice with benzene (total volume, 800 ml). The benzene extracts and the separated organic layer were combined. The solution was placed in a flask on a rotoevaporator. Benzene, $H_2O$, and any other readily volatile fractions were removed. The residue was transferred to a flask large enough to permit vigorous stirring by a magnetic stirrer. The sample was vacuum distilled using a 200 mm Vigreaux column. The fractions were analyzed by gas chromatography. All fractions of a purity better than 90% were combined. The desired 4-chlorobenzalacetone was recovered at 112-116°, 0.6-0.4 mm. Total weight was 150 g, or 77% yield.

4-(4-Chlorophenyl)-5-phenyl-2-pentanone, 36.

An oven dried 3 neck 3 liter flask was equipped with a mechanical stirrer, reflux condenser with drying tube, and dropping funnel.

The apparatus was flushed with nitrogen. The flask was charged with dry Mg turnings (20.0 g, 825 mmol) and sodium-dried ether (100 ml). The dropping funnel was charged with benzyl chloride (99.6 g, 790 mmol) in dried ether (150 ml). A small amount of this solution was added to the Mg to start the reaction, evidenced by the appearance of a white turbidity in the ether. The reaction mixture was diluted with a large quantity (1500 ml) of ether. The remainder of the benzyl chloride solution was added at such a rate that 1 to 2 drops per sec reflux rate was maintained while cooling the flask and contents in ice $H_2O$. When addition was complete, heat was applied, and reflux was continued for 15 to 20 min. The reaction mixture was cooled below -20 to -30° in a dry ice-acetone bath. A solution of 4-chlorobenzalacetone (60.0 g, 334 mmol) and cupric acetate monohydrate (16.8 g, 83.6 mmol) in dry tetrahydrofuran (700 ml) was added at such a rate as to keep the temperature of the reaction mixture below -30°. Initially the thick mixture became brick red. As addition continued, the color gradually darkened to brown. After addition was completed, the reaction mixture was stirred overnight and was allowed to warm to room temperature. By this time, the mixture had a definite copper color. The contents were refluxed for 1 hour. The complex was then decomposed by the addition of saturated $NH_4Cl$ solution. Just enough solution was added to form a viscous mass in the bottom of the flask, from which the ether solution could be decanted. After decantation of the ether layer, the remaining mass was

washed with fresh ether (200 ml). The ether fractions were combined. The resulting ether solution was extracted with a dilute $Na_2S_2O_3$ solution to remove any residual cuprous ion. The ether solution was washed with $H_2O$ and was dried over $Na_2SO_4$. The solvent was removed on a rotoevaporator. The residue was partially vacuum distilled to remove the diphenylethane. The residue was dissolved in the minimum amount of boiling hexane, and a product was allowed to crystallize in the refrigerator. The crude product was filtered, and some attempts were made to purify it by crystallization from MeOH, hexane, and MeOH-hexane mixtures. The crude material was subjected to a series of triturations with cold MeOH, and then cold hexane. The purity of the sample was monitored by gas chromatography. A product was obtained that contained less than 5% total impurity. The weight was 27.7 g, or 30.4% yield. A small sample, crystallized from hexane, melted at 96-97°.

Anal. Calcd. for $C_{17}H_{17}ClO$: C, 74.86; H, 6.28; Cl, 13.00. Found: C, 75.10; H, 6.32; Cl, 13.15.

In earlier work the product was purified for further steps by vacuum distillation (170-180°, 0.6 mm). This did not produce as pure a material as the above procedure, but yields were close to 60%.

Cyclization of 4-(4-chlorophenyl)-5-phenyl-2-pentanone

A mixture of 4-(4-chlorophenyl)-5-phenyl-2-pentanone (27.7 g, 103 mmol) and polyphosphoric acid (100 g) was placed in a flask. The flask was evacuated with a water aspirator. The flask and contents were gradually heated to 200° (2 hr) in an oil bath. A magnetic stirrer was used to stir the mixture once the temperature of the mixture rose above 100°. Samples were taken to follow the disappearance of the carbonyl band in the ir spectrum. After 2 hr at 200°, the carbonyl band disappeared from the ir spectrum. The reaction was assumed to be complete. The contents of the flask were poured into 1 liter of $H_2O$. The gummy suspension was extracted with ether (600 ml), and the ether solution was washed cautiously with a dilute $NaHCO_3$ solution. The ether layer was washed with $H_2O$ and was dried over $Na_2SO_4$. Removal of the solvent left 25.6 g of product mixture. Analysis of this mixture by gas chromatography showed the following composition: 3-(4-chlorophenyl)-1-methylnaphthalene, 33%; 3-(4-chlorophenyl)-1-methyl-1, 2, 3, 4-tetrahydronaphthalene, 50.5%; 5,10-methano-7-chloro-5-methyldibenzo(a, d) cycloheptane, 16.5%. The mixture was carried on to the next step without further purification.

Crystallization of a product from an earlier experiment resulted in a pure sample of 5,10-methano-7-chloro-5-methyl-dibenzo(a, d) cycloheptane, which melted at 135-138°.

Anal. Calcd. for $C_{17}H_{15}Cl$: C, 80.15; H, 5.93; Cl, 13.92; Found: C, 80.24; H, 5.92; Cl, 13.91.

3-(4-Chlorophenyl)-1-methylnaphthalene, 41.

The mixture (26.5 g) from the previous procedure was heated with sulfur (3.5 g) under water aspirator vacuum, to 260° in a fused salt bath. After 1.5 hr a sample was taken and was analyzed by gas chromatography. Some of the tetrahydronaphthalene appeared to be present. More sulfur (0.5 g) was added, and the reaction was continued as before for 0.5 hr. An analysis was made by gas chromatography. The composition of the mixture was: 3-(4-chlorophenyl)-1-methylnaphthalene, 80%; 3-(4-chlorophenyl)-1-methyl-1,2,3,4-tetrahydronaphthalene, <9%; 5,10-methano-7-chloro-5-methyl-dibenzo (a,d) cycloheptane, 11.5%. The residue was dissolved in ether and was stirred vigorously with mercury for 3 hr to remove excess sulfur. The solution was filtered to remove the HgS and mercury. The solution was stirred with mercury again overnight. The solution was filtered to remove more HgS and Hg. The solvent was removed. The residue was vigorously stirred under vacuum (0.05-0.02 mm) and heated to 135°. Under these conditions the methanocycloheptane compound sublimed. Within 2 hr, less than 1% remained in the flask, leaving 19 g crude aromatic compound. The crude material was vacuum

distilled (152°, 0.06 mm) to recover the purified 3-(4-chlorophenyl)-1-methylnaphthalene. The weight was 14 g, or 54% yield from the pentanone. The structure was confirmed by nmr.

3-(4-Chlorophenyl)-1-naphthaldehyde, 42.

3-(4-Chlorophenyl)-1-methylnaphthalene (6.3 g, 25 mmol) was placed in a flask with triglyme (30 ml), and the solution was refluxed. $SeO_2$ (2.8 g, 25 mmol) dissolved in a minimum amount of $H_2O$ was added cautiously and portionwise over a period of 2 hr. A check of the reaction mixture by gas chromatography showed a considerable amount of starting material. Twice again solutions of $SeO_2$ (1 g) in $H_2O$ were added. The mixture was allowed to sit over the weekend. It was refluxed for 5 hr more. Analysis of the reaction mixture by gas chromatography showed 7% starting material and 93% product. The reaction mixture was filtered to remove selenium and excess $SeO_2$. The filtrate was stirred with Raney nickel for 2 hr to remove any residual selenium. The resulting triglyme suspension was filtered, and the filtrate was poured into $H_2O$ and allowed to stand. The cloudy $H_2O$ was decanted, and the remaining solid was crystallized from an acetone-$H_2O$ mixture. The recovered 3-(4-chlorophenyl)-1-naphthaldehyde melted at 119-121°. The weight was 3.8 g, or 56% yield.

Anal. Calcd. for $C_{17}H_{11}ClO$: C, 76.55; H, 4.16, Cl, 13.29. Found: C, 76.42; H, 4.25; Cl, 12.58.

4-(4-Chlorophenyl)-1-(1,2-epoxyethyl)-naphthalene, 43.

A dry 3 neck flask was equipped with a magnetic stirrer, dropping funnel, gas inlet and outlet, and was protected with a $CaCl_2$ drying tube. The assembled apparatus was swept with nitrogen. An oil dispersion of NaH (0.92 g, 22 mmol, 57% dispersion) was put into the flask and was washed with pentane. This removed the mineral oil. The NaH was dried by sweeping the flask with a rapid flow of nitrogen. Dimethylsulfoxide (DMSO) (6 ml) was added. The flask was heated to 70° in a hot $H_2O$ bath for 1 hr. Tetrahydrofuran (THF) (100 ml) was added, and the resulting solution was refluxed for 1.5 hr. The flask and contents were cooled below 0°. Trimethylsulfonium iodide (4.35 g, 21 mmol) in DMSO (35 ml) was added dropwise in 10-15 min. The temperature of the reaction mixture was kept below 0° during the addition. After addition, the thick mixture was stirred for 10 min. A tube was inserted into the flask so that pressurizing the flask with nitrogen forced the contents through the tube and into a flask containing a stirred solution of 3-(4-chlorophenyl)-1-naphthaldehyde (5.0 g, 18.8 mmol) in dry THF. The flask had been swept with nitrogen previously. The resulting solution was stirred at room temperature for 2 hr. Examination of the reaction mixture by gas chromatography indicated that 90% of the product was the desired 3-(4-chlorophenyl)-1-(1,2-epoxyethyl)-naphthalene. The reaction mixture was poured into $H_2O$ (3 liters). The suspension was ex-

tracted 3 times with ether, and all extracts were combined (1500 ml). The ether solution was washed with $H_2O$ and was dried with $Na_2SO_4$ overnight. The ether was removed. The viscous oil was used without further purification. The weight was 5.8 g. Chromatographic analysis showed the material to be 90% pure 3-(4-chloropenyl)-1-(1,2-epoxyethyl)-naphthalene. Thus, a corrected yield was 5.2 g, or 98%.

3-(4-Chlorophenyl)-α-dibutylaminomethyl-1-naphthalenemethanol hydrochloride, 8.

A mixture of 3-(4-chlorophenyl)-1-(1,2-epoxyethyl)-naphthalene (5.8 g, 18.5 mmol; 90% pure) and dibutylamine (13 g, 100 mmol) was placed in a flask under nitrogen atmosphere. The mixture was stirred and was heated to reflux (160°) for 24 hr. Examination of the mixture by thin layer chromatography showed a very small spot at the position of the epoxyethylnaphthalene. The dibutylamine was removed by distillation under reduced pressure. The residue was dissolved in ether (600 ml). Ethereal HCl (1 N) was used to fractionally precipitate the basic components of the solution. Melting points were used to monitor the purity and composition of the fractions. Residual dibutylamine hydrochloride was precipitated first and was discarded. Next 4.0 g of the product was precipitated. It melted at 201-203°. A few smaller and less pure samples were precipitated. These latter samples were combined and were washed with acetone to yield 0.5 g of product melting at 205-207°. This

was a combined crude yield of 4.5 g, or 55%. The largest sample washed with acetone to leave 3.1 g of product melting at 206-207°. ---- and the 0.5 g sample were combined and were dissolved in chloroform (75 ml). The solution was concentrated by boiling. A quantity of acetone was added, and the product was allowed to crystallize in the refrigerator. Filtration and drying left 3-(4-chlorophenyl)-α-dibutylaminomethyl-1-naphthalenemethanol hydrochloride melting at 206-209°. The weight was 3.2 g, or 39% purified yield.

Anal. Calcd. for $C_{26}H_{33}Cl_2NO$: C, 69.95; H, 7.45; N, 3.14; Cl, 15.88. Found: C, 69.92; H, 7.40; N, 3.30; Cl, 15.70.

3-(4-Chlorophenyl)-α-diheptylaminomethyl-1-naphthalenemethanol hydrochloride, 9.

A mixture of 3-(4-chlorophenyl)-1-(1,2-epoxyethyl)-naphthalene (4.2 g, 15 mmol) and diheptylamine (12 g, 56 mmol) was placed in a flask under nitrogen atmosphere. The mixture was stirred and was heated to 170° over the weekend. The residue was heated at 150° and 0.1 mm pressure to remove the diheptylamine. The residue was dissolved in ether (400 ml). The residual diheptylamine was removed by the addition of ethereal HCl (1.2 N, 2 ml). Further addition of ethereal HCl (14 ml) precipitated a crude product melting at 145-148°. The weight was 4.7 g, or 62% crude yield. The sample was crystallized from a chloroform-acetone mixture. The resulting product was crys-

tallized from acetone. Filtration and drying left 3-(4-chlorophenyl)-α-diheptylaminomethyl-1-naphthalenemethanol hydrochloride melting at 154-156°. The weight was 3.1 g, or 41% purified yield.

Anal. Calcd. for $C_{32}H_{45}Cl_2NO$: C, 72.43; H, 8.55; N, 2.64; Cl, 13.36. Found: C, 72.44; H, 8.49; N, 2.66; Cl, 13.31.

3-(4-Chlorophenyl)-α-diethylaminomethyl-1-naphthalenemethanol hydrochloride, 7.

A mixture of 3-(4-chlorophenyl)-1-(1,2-epoxyethyl)-naphthalene (2.0 g, 6.4 mmol) and diethylamine (7.8 g, 106 mmol) was placed in a stainless steel bomb. The bomb was heated to 120° for 4 days. The contents of the cooled bomb were dissolved in ether. The ether and diethylamine were removed in a rotoevaporator. The residue was dissolved in ether, and was treated with activated charcoal (Norit A). The charcoal was removed by filtration. Fractional precipitation with ethereal HCl (1.2 N) gave a product melting at 152-156°. The weight was 1.5 g. The sample was twice crystallized from acetone. Filtration and drying left 3-(4-chlorophenyl)-α-diethylaminomethyl-1-naphthalenemethanol hydrochloride melting at 156-159°. The weight was 0.8 g, or 23.5% purified yield.

Anal. Calcd. for $C_{22}H_{25}Cl_2NO$: C, 67.69; H, 6.46; N, 3.59; Cl, 18.16. Found: C, 67.56; H, 6.20; N, 3.55: Cl, 18.37.

3-(4-Chlorophenyl)-7-methoxy-1-naphthaldehyde, 44.

3-(4-Chlorophenyl)-7-methoxy-1-naphthalene (5.0 g, 18 mmol) was placed in a flask with triglyme (50 ml) and the solution was refluxed. $SeO_2$ (2.15 g, 19 mmol) dissolved in a minimum amount of $H_2O$ was added cautiously. The mixture was refluxed overnight. Analysis of the reaction mixture by gas chromatography indicated 50% conversion. Two successive additions of $SeO_2$ (1 g) in $H_2O$ were made. Conversion reached 85%. The solution was cooled and was poured into $H_2O$. The suspension was extracted with chloroform. The chloroform was removed. The residue was triturated with ether. The remaining solid weighed 3 g. A solid crystallized from the ether. The two samples were combined and were dissolved in benzene. The benzene solution was stirred with Raney nickel. The benzene solution was concentrated, and a sample of 3-(4-chlorophenyl)-7-methoxy-1-naphthaldehyde crystallized. It melted at 163-165°. The weight was 1.9 g, or 36% yield.

Anal. Calcd. for $C_{18}H_{13}ClO_2$: C, 72.86; H, 4.41; Cl, 11.95. Found: C, 72.93; H, 4.41; Cl, 11.75.

3-(4-Chlorophenyl)-1-(1,2-epoxyethyl)-7-methoxynaphthalene, 45.

A dry 3 neck flask was equipped with a magnetic stirrer, dropping funnel, gas inlet and outlet, and was protected with a $CaCl_2$ drying tube. The assembled apparatus was swept with nitrogen. An oil dispersion of

NaH (0.185 g, 4.4 mmol, 57% dispersion) was placed in the flask and was washed with pentane. This removed the mineral oil. The NaH was dried by sweeping the flask with a rapid stream of nitrogen. DMSO (2 ml) was added. The flask was heated to 70° in a hot water bath for 1 hr. THF (20 ml) was added, and the resulting solution was refluxed for 2 hr. The flask and contents were cooled below 0°. Trimethysulfonium iodide (0.875 g, 4.2 mmol) in DMSO (7 ml) was added dropwise in 5 min. The temperature of the reaction mixture was kept below 0° during the addition. After the addition the mixture was stirred for 10 min. A tube was inserted into the flask so that pressurizing the flask with nitrogen forced the contents through the tube and into a flask containing a stirred solution of 3-(4-chlorophenyl)-7-methoxy-1-naphthaldehyde (1.1 g, 3.7 mmol) in dry THF. The flask had been swept with nitrogen previously. The resulting solution was stirred at room temperature for 2 hr. The reaction mixture was poured into $H_2O$(500 ml). The suspension was extracted with ether. The ether solution was washed with $H_2O$ and was dried with $Na_2SO_4$. The ether was removed. Weight of the product was 0.9 g, or 95% yield. It was carried to the next step without further purification.

3-(4-Chlorophenyl)-α-dibutylaminomethyl-7-methoxy-1-naphthalene-methanol hydrochloride, 11.

A mixture of 3-(4-chlorophenyl)-1-(1,2-epoxyethyl)-7-methoxy-naphthalene (0.9 g, 2.9 mmol) and dibutylamine (7.6 g, 50 mmol) was placed in a flask under nitrogen atmosphere. The mixture was stirred and heated to reflux (160°) for 24 hr. The reaction mixture stood at room temperature over the weekend. The dibutylamine was removed by vacuum distillation. The residue was dissolved in ether, and ethereal HCl (1.2 N) was added to precipitate the product as the hydrochloride. A crude product was recovered that melted at 213-215° and weighed 1.0 g. The product was dissolved in an acetone-chloroform mixture and was allowed to crystallize. Filtration and drying left a pure sample of 3-(4-chlorophenyl)-α-dibutylaminomethyl-7-methoxy-naphthalene-methanol hydrochloride melting at 221-222°. The weight was 0.7 g, or 50% yield.

Anal. Calcd. for $C_{27}H_{35}Cl_2NO_2$: C, 68.06; H, 7.40; N, 2.94. Found: C, 68.08; H, 7.45; N, 3.03.

3,4-Dichlorobenzalacetone, 46.

A 2 liter 3 neck flask was equipped with a thermometer, dropping funnel, and mechanical stirrer. The flask was charged with 3,4-dichloro-benzaldehyde (175 g, 1 mol) and reagent grade acetone (550 ml). The

solution was cooled in an ice bath to 10°. A solution of NaOH (2.8 g) in $H_2O$ (55 ml) was added dropwise. After 2/3 of the basic solution was added, the solution turned yellow, and the temperature began to rise rapidly. The temperature reached 14°. Addition was continued at such a rate as to prevent any further rise in temperature. The reaction was monitored by gas chromatography. After 3 hr the mixture showed a 50-50 mixture of starting material and reaction product. The solution was allowed to stir at room temperature overnight. The solution became very dark. Analysis of the solution showed a 40-60 mixture of starting material and product. Dilute HCl was added until the contents of the flask were acidic. The acetone was removed from the mixture by evaporation in a rotoevaporator. The temperature of the mixture was kept below 40°. $H_2O$ was added to the residue and the resulting mixture was extracted with benzene. The benzene, $H_2O$, and any other volatile component were removed by evaporation in a rotoevaporator. The mixture was heated in a boiling water during the evaporation. A glassy solid remained. Vacuum distillation of this product yielded 50 g of very crude product. The sample was crystallized from ether. A sample of 3,4-dichlorobenzalacetone weighing 19.2 g was obtained. Further crystallization resulted in 3.4 g of less pure material. The structure of both samples was confirmed by nmr.

## SUMMARY

Reactions of the proposed synthetic pathways leading to three series of the α-dialkylaminomethyl-1-naphthalenemethanols were studied. Two synthetic pathways were proposed.

Failure of the Ullmann synthesis under cited conditions eliminated one synthetic route immediately.

The 3-(4-chlorophenyl)-α-dialkylaminomethyl-1-naphthalenemethanols were prepared in a complete study of the second synthetic method. Although three target compounds were prepared, considerable time and effort was spent in obtaining practical yields and reasonably pure intermediates. The overall yield was poor.

Study of the 3-(4-chlorophenyl)-α-dialkylaminomethyl-7-methoxy-1-naphthalenemethanols was shortened by a supply of a key intermediate prepared in our laboratory previously. Again, practical yields of pure compounds were prepared with difficulty. One target compound was prepared.

Preparations of the 7-chloro-3-(3,4-dichlorophenyl)-α-

dialkylaminomethyl-1-naphthalenemethanols was not successful due to failure of early stages to yield usably pure intermediates.

Complete biological data were available for the 3-(4-chlorophenyl)-α-dibutylaminomethyl-1-naphthalenemethanol only. The compound showed remarkable antimalarial activity, and was not phototoxic.

It would appear that the synthetic pathways studied were not successful as universal methods of obtaining the desired naphthalene-methanols. However, in light of the activity of the cited compound, as indicated from the data available, further studies toward better pathways to the 3-phenyl-α-dialkylaminomethyl-1-naphthalenemethanols would seem desirable.

## References


1. Geiman, Q. M., N. Engl. J. of Med., 239, No. 1, 18 (July 1, 1948).

2. Dennis, E. W. and Berberian, D. A., Ann. Rev. Med., 4, 345 (1953).

3. World Health Organ. Tech. Rept. Ser., No. 296, 13 (1965).

4. Most, H., Mil. Med., 129, 587 (1964), edited by R. M. Pinder in "Medicinal Chemistry", 3rd ed. A. Burger, Ed., Wiley-Interscience, New York (1970), Chapter 20.

5. Sweeney, T. R. and Jacobus, D. P., from a paper presented at the 12th Nat. Sym. on Med. Chem., Seattle, Washington (June 21-25, 1970).

6. Pinder, R. M. in "Medicinal Chemistry", 3rd ed., A. Burger, Ed., Wiley-Interscience, New York (1970), Chapter 20.

7. Lutz et al., J. Amer. Chem. Soc., 68, 1813 (1946).

8. Winstein et al., ibid., 68, 1831 (1946).

9. Campbell et al., ibid., 68, 1837, 1840, 1844 (1946) inter alia.

10. Wiselogle, F. Y., Ed., "A Survey of Antimalarial Drugs, 1941-1945", J. W. Edwards, Ann Arbor, Mich., 1946.

11. Coatney, G. R., "Survey of Antimalarial Drugs", Public Health

Service Monograph No. 9, Federal Security Agency, 1952; also known as Public Health Service Publication No. 193.

12. Burger, A., "Medicinal Chemistry", Interscience Publishers Inc., New York (1951), p. 762.

13. Gillespie, J. S., Jr., Rowlett, R. J., Jr., and Davis, R. E., J. Med. Chem., 11, 425 (1968).

14. Rothe, W. E. and Jacobus, D. P., J. Med. Chem., 11, 366 (1968).

15. Gillespie, J. S., Jr., Acharya, S. P., Davis, R. E., and Barman, B. F., J. Med. Chem., 13, 860 (1970).

16. Burger, A., Ed., in "Medicinal Chemistry", 3rd ed., Wiley-Interscience, New York (1970), Chapter 6.

17. Kirshbaum, B. A. and Beerman, H., Amer. J. Med. Sci., 248, 117/445 (1964).

18. Ison, A. and Blank, H., J. Inves. Derm. 49, No. 5, 508 (1967).

19. Willis, I. and Kligman, A. M., ibid, 51, No. 2, 116 (1968).

20. Fels, I. G., J. Med. Chem., 11, 887 (1968).

21. May, E. L. and Mosettig, E., J. Org. Chem., 11, 1 (1946).

22. Jacobs, T. L., et al., J. Org. Chem., 11, 21 (1946).

23. Winstein, S., et al., ibid., 11, 150 (1946).

24. Winstein, S., et al., ibid., 11, 157 (1946).

25. Atkinson, E. R. and Puttick, A. J., J. Med. Chem., 11, 1223 (1968).

26. Parikh, J. R. and Doering, W. von E., J. Amer. Chem. Soc., 89, 5505 (1967).

27. Corey, E. J. and Chaykovsky, M., ibid., 87, 1352 (1956).

28. Kaplan, H., J. Amer. Chem. Soc., 63, 2654 (1941).

29. Zinke, T. and Breuer, A., Ann., 226, 23 (1884), as cited in C. K. Bradsher, Chem. Rev. 38, 447 (1946).

30. Auwers, K. von and Keil, G., Ber., 36, 3902 (1903).

31. Spring, F. S., J. Chem. Soc., 1934, 1332.

32. Quillet, J. P. and Dreux, J., Bull. Soc. Chim. France, 1966, 645.

33. Fanta, Chem. Rev., 38, 139 (1946).

34. Gore, P. H. and Hughes, G. K., J. Chem. Soc., 1615 (1959).

35. Morrison, R. T. and Boyd, R. N., "Organic Chemistry", Allyn and Bacon Inc., Boston, 1959, p. 821.

36. Bigelow, L. A. and Reynolds, H. H., in "Organic Syntheses", Coll. Vol. 1, H. Gilman, Sr., Ed., John Wiley and Sons, Inc., New York, 1932, p. 476.

37. Drake, N. L. and Allen, P., Jr., in "Organic Syntheses", Coll. Vol. 1, H. Gilman, Sr., Ed., John Wiley and Sons, Inc., New York, 1932, p. 77.

38. Marshall, J. A., Fanta, W. I., and Roebke, H., J. Org. Chem., 31, 1016 (1966).

39. Kharasch, M. S. and Tawney, P. O., J. Amer. Chem. Soc., 63, 2308 (1941).

40. Birch, A. J. and Smith, M., Proc. Chem. Soc., 356, (1962).

41. Munch-Petersen, J. and Andersen V. K., Acta Chem. Scand., 15, 271 (1961).

42. Kharasch, M. S. and Reinmuth, O., "Grignard Reactions of Non-metallic Substances", Prentice-Hall, Inc., New York, 1954, p. 228.

43. Fieser, L. F. and Fieser, M., "Reagents for Organic Synthesis", John Wiley and Sons, Inc., New York, 1967, p. 894.

44. Ref. No. 42, p. 1118.

45. Ref. No. 41, p. 20.

46. Ref. No. 41, p. 17.

47. Ref. No. 41, p. 221.

48. Melton, R. G. et al., Org. Prep. and Proced., 2, 37 (1970).

49. Steck, E. A., personal communication, 1971.

50. Test procedure is described by Osdene, T. S., Russell, P. B., and Rane, L., J. Med. Chem., 10, 431 (1967).

# AUTOBIOGRAPHY

I, Richard Elroy Davis, was born in Richmond, Virginia on August 15, 1939. I graduated from Will Rogers High School, Tulsa, Oklahoma, in 1957. I attended the University of Maryland from 1957 to 1958. I attended Baltimore Junior College from 1958 to 1959. In September of 1959 I entered the University of Richmond. I graduated with a Bachelor of Science degree in June of 1962. I attended the Graduate School of the University of Richmond as a full-time student from 1962 to 1963. In June of 1963 I became a full-time employee of the Virginia Institute for Scientific Research. From that time to the present, I have remained a full-time employee at VISR and a part-time student in the Graduate School.