CHEMOTHERAPEUTIC AGENTS IN THE QUINOLINOL SERIES

by

William H. Edgerton
B.S., University of Connecticut, 1945

Submitted to the Department of Pharmacy and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Advisory Committee:

Redacted Signature

Chairman

Redacted Signature

Redacted Signature

Redacted Signature

Redacted Signature

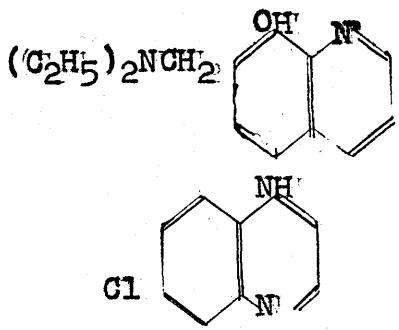
February, 1950

The author wishes to thank his wife for her understanding, Dr. J. H. Burckhalter for his direction and patience, and Parke, Davis & Co. for financial aid.

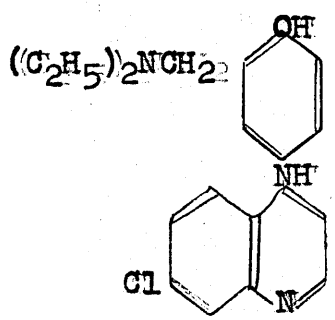
CONTENTS

I. INTRODUCTION

An attempt has been made by others[1] to synthesize XVI



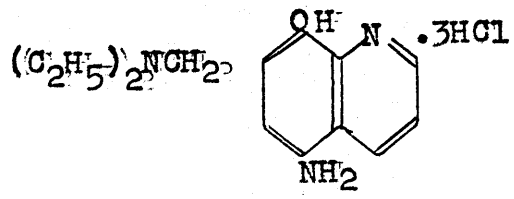
XVI



Camoquin

with the prospect of obtaining an analogue of the antimalarial, Camoquin[2], which might be even more promising. Its formula possesses more of the structural features required for gametocidal activity by the Schönhöfer theory[3] than does Camoquin.

Despite the earlier unsuccessful attempts[1] to obtain XVI, the intermediate III was screened for possible antimalarial activity because it, too, possesses the structural features for intrinsic effectiveness required by the Schönhöfer theory. III was found to have antimalarial activity in avian malaria; however, the activity found in an <u>impure</u> sample of III appeared to diminish appreciably upon purification. Concerning the effectiveness of the impure III



III

Dr. Paul G. Thompson, pharmacologist of Parke, Davis & Co., said: "At even the MED [minimal effective dose] the parasites are completely annihilated. Indeed, it is difficult to find even traces of parasites in the blood smears."

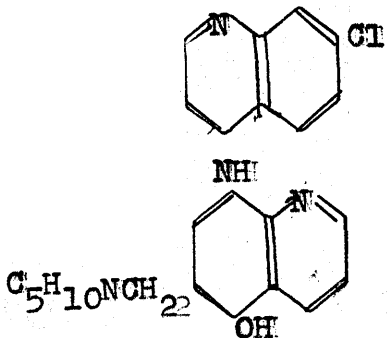
The problem of the activity of impure III could perhaps be resolved into two possibilities:

1. Activity of an impurity, either a by-product or starting material which was carried along in the reaction.

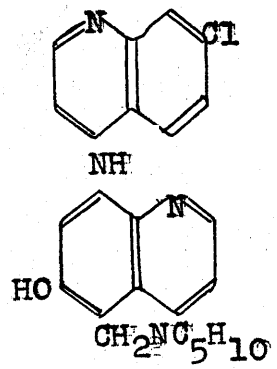
2. Activity inherent in the compound itself with the observed decrease in activity attributable to vagaries in the method of pharmacological testing.

Thus it seemed advisable to investigate thoroughly both the chemical and pharmacological aspects of the lead. The pharmacological studies were to be conducted by Dr. Thompson.

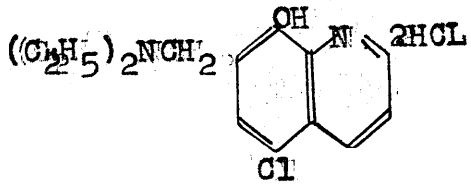
The objective of the present chemical studies includes the synthesis of XVI and the analogous compounds, XXVI and XXXII, all designed as possible antimalarial agents, as well as other derivatives and relatives of III such as XLVII, XLIX, a, LIII, LVI, and LIX.



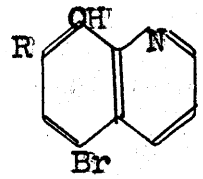
XXVI



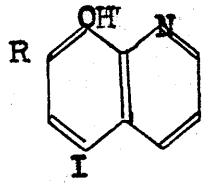
XXXII



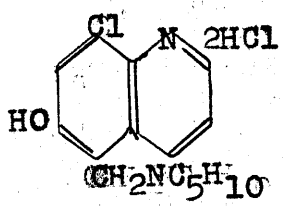
XLVII



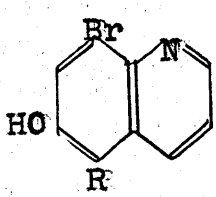
XLIX



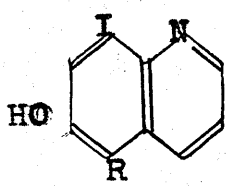
a



LIII

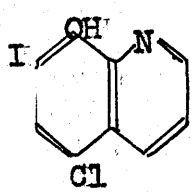


LVI

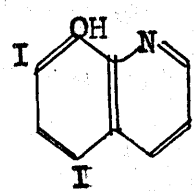


LIX

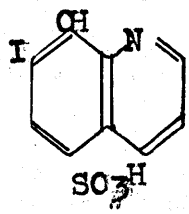
These latter compounds, XLVII to LIX, inclusive, might be expected to possess amebacidal activity, since they have structural resemblance to well known amebacides such as Vioform, Diodoquin, and Chiniofon.



Vioform

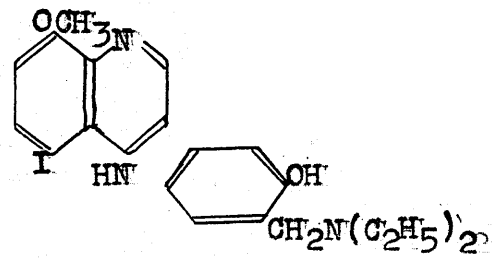


Diodoquin



Chiniofon

Further, because of the known amebacidal activity of the 4-aminoquinoline antimalarials[4] (represented by Camoquin), it was decided to prepare such a compound as LXXIV which not only is a 4-aminoquinoline but also possesses



LXXIV

the quinolinol nucleus of the amebacides, XLVII to LIX. Thus, LXXIV is a hybrid of both the compounds synthesized for antimalarial and for amebacidal purposes in the present studies. The biological activity of such a product would, therefore, be of considerable interest.

II. HISTORICAL

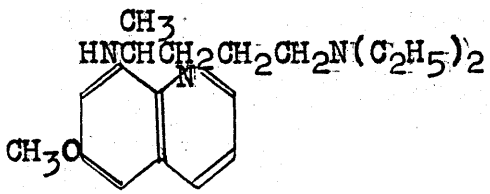
Antimalarial Agents[5,6]

Great progress outside the field of chemotherapy has been made in the fight against human malaria with the widespread use of the revolutionary insecticide, DDT, for killing anopheline mosquitoes. While such preventive measures are important, they neither solve the problem nor eliminate the need for improved antimalarial drugs which will be highly effective against the disease and yet only slightly toxic to the patient.

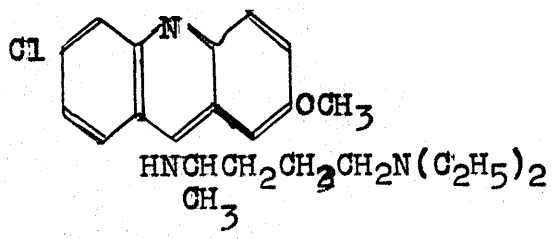
The four parasites which cause human malaria are Plasmodium malariae, P. ovale, P. falciparum, and P. vivax. Only malarias caused by the last two species will be considered in this discussion because of their paramount importance. P. falciparum is the causative parasite in malignant tertian malaria. Its attacks which may be fatal are characterized by an increase in temperature every 36-48 hours. The symptoms, if properly treated, are unlikely to recur. P. vivax is the causative parasite in benign tertian malaria. Its attacks are seldom fatal and have 36-hour rises in temperature. The symptoms recur periodically, often over long lapses of time.

The Peruvian aborigines used the back of the cinchona tree empirically to treat malaria. The spread of

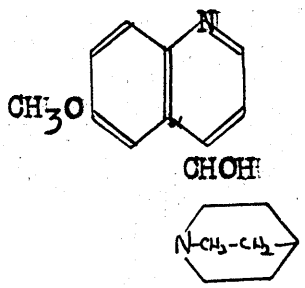
the use of the drug extract over Europe led to the isolation of the active ingredient, quinine, in 1820 by Pelletier and Caventou. Methylene blue was the first synthetic drug to exhibit antimalarial activity experimentally, in the laboratories of Ehrlich. This key observation mushroomed into the healthy research program of the I. G. Farbenindustrie which produced the following active synthetic plasmodicides: pamaquine (Plasmochin[a]) in 1924, quinacrine (Atabrine) in 1930, and finally the 4-aminoquinoline group including chloroquine (Resochin) in 1939. In the progress of this program, the German workers produced and tested over 1200 compounds.



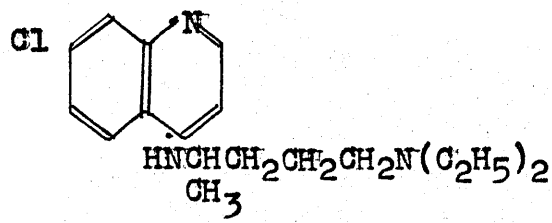
Plasmochin



Atabrine



Quinine



Chloroquine

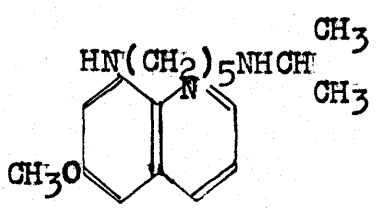
---

a It should be noted that trade names are capitalized. In the present discussion, the most commonly known name, either trade or generic, is used.

After the outbreak of World War II, a tremendous integrated program was launched by the Government of the United States under the Office of Scientific Research and Development to re-evaluate the German discoveries and to synthesize a substitute for quinine since the main sources of the latter drug, including the Netherlands Indies, had fallen to the Japanese. The net result of the war work has been summarized in a three volume monograph.[7]

The practical re-evaluation of the German compounds established the fact that the I. G. Farben antimalarial drugs, which were open to Allied manufacture since they were produced before the outbreak of the war, were sufficiently effective to control human malaria.[5] Atabrine was declared to be superior to quinine chemotherapeutically although its use imparted a yellow tint to the skin. Plasmochin was found to cure vivax malaria but was too toxic for general use. Chloroquine was even more effective and useful than the Germans had reported originally.

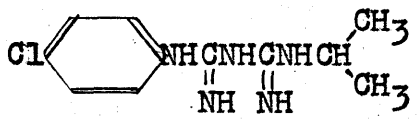
One of the synthetic antimalarials produced in the United States under the war program was pentaquine, an 8-aminoquinoline which is structurally similar to Plasmochin.



Pentaquine

This drug, used in conjunction with quinine and administered under close supervision in a hospital, will cure the relapsing type of malaria. The 4-aminoquinolines, represented by chloroquine, are considered to be superior in vivax malaria to Atabrine, essentially a 4-aminobenzoquinoline.

Toward the end of World War II, the British introduced an inexpensive, nontoxic drug named chlorguanide (Paludrine), which presented a startling development since



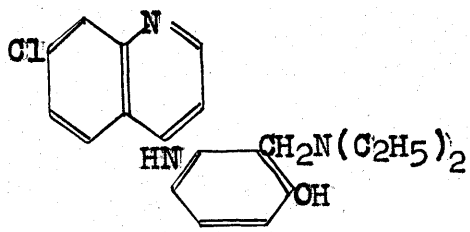
Paludrine

it is a prophylactic for falciparum malaria and a partial prophylactic for vivax malaria.[8] In addition, the structure of Paludrine is completely different from that of any of the plasmodicidal compounds previously known. Unfortunately, Paludrine does not possess action rapid enough to control an acute attack of the disease,[9] and it also shows a definite tendency to lose its effectiveness against certain species of the protozoan parasite.[10] Furthermore, it does not cure relapsing malaria caused by Plasmodium vivax.

Many of the more important antimalarials which have successfully withstood clinical trial contain the

quinoline or benzoquinoline nucleus. Paludrine is a notable exception. The quinoline derivatives are generally considered to be the drugs of choice in the treatment of malaria except where a true prophylactic is desired. Further, the 4-aminoquinolines are administered for an acute attack of malaria (falciparum); a combination of an 8-aminoquinoline and quinine for relapsing malaria (vivax).

One of the 4-aminoquinolines which has shown exceptional activity against avian and human malaria is Camoquin[2]. Since Camoquin is a phenolic Mannich base, a



Camoquin

logical step forward in the chemotherapy of this family of drugs would be the synthesis of various quinolyl Mannich bases, several of which are discussed in later sections.

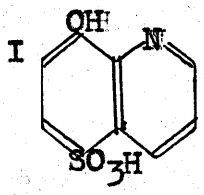
Amebacidal Agents[11,12,13]

Amebiasis is a disease caused by invasion of the tissues of man by the pathogenic ameba, Endameba histolytica. The parasite is carried from man to man by food or drink which is infested with the cyst form of its life cycle. The motile forms of the parasite are activated in the large intestine and invade the tissues by boring through the mucosa of the intestinal wall. The parasite may then cause abscess formation, most often in the liver but occasionally in the brain, lungs or kidneys. Thus the toxic manifestations of amebiasis may be divided into two groups: those caused by gastric upset and those caused by abscess formation.

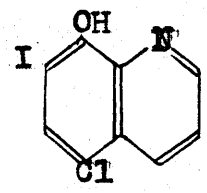
The disease is world-wide and has been particularly troublesome during war. About 5 to 10 per cent of the population of the United States is said to be infected, either as active cases or as carriers. Amebiasis is endemic in the southern states.

The causative organism, Endameba histolytica, was discovered in 1875 by Lösch in the dysenteric stools of a patient in St. Petersburg. Emetine, which was detected in ~~cinchona bark~~ ipecac bark by Pelletier and Magendie in 1817, was first used extensively in dysentery and hepatitis by Rogers in 1922. Many drugs have been used in amebiasis since that time but no single drug has proved consistently acceptable chemotherapeutically in both phases of amebiasis.

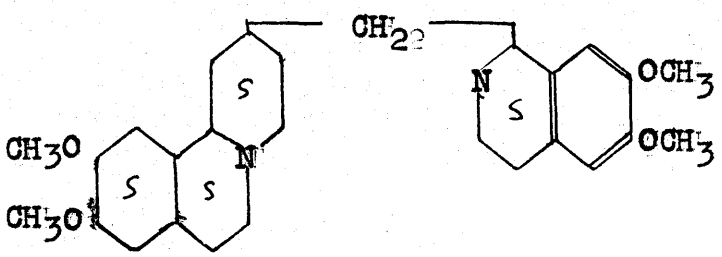
Among the quinoline derivatives which have been introduced for treating intestinal amebiasis are Chiniofon, Vioform, and Diodoquin. All these drugs are of the same



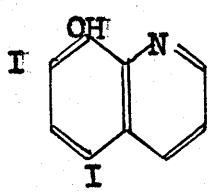
Chiniofon



Vioform



Emetine[51]



Diodoquin

order of effectiveness and are quite non-toxic. While the quinolines are excellent remedies for intestinal amebiasis, no one drug is effective in every case[14]. The efficiency of the compounds is said to be due to the available halogen content. Among other non-quinoline drugs used are the pentavalent arsenicals: Carbarsone, Treparsol, Acetarsone, and Milibis.

For many years the only drug used consistently for extraintestinal lesions was emetine[15]. Surgery was often

resorted to because of the lack of proper chemotherapeutic relief. Although emetine relieves about 85 per cent of the acute symptoms, the number of cured cases ranges only from 10 to 15 per cent[4c,13,15]. Further, the patient should be hospitalized during the course of treatment because of the toxicity of the drug. Many of the alkaloids which are effective amebacides are also cardiac poisons (conessine, etc.)[17].

Reports of the use of antibiotics in the treatment of amebiasis have appeared lately[18]. Penicillin, aureomycin, and bacitracin have been found to be active. Although information about clinical results of the antibiotics is fragmentary, it is to be expected that their chief use would probably be confined to combatting secondary bacterial infections which invariably accompany amebacidal infection.

In the last few years, certain antimalarial drugs, of which the 4-aminoquinolines should be mentioned, have exhibited effectiveness in hepatic amebiasis[4]. Chloroquine has been proved clinically to be at least as effective as emetine and much less toxic. While the 4-aminoquinolines have shown usefulness in extraintestinal amebiasis, an intestinal amebacide is needed as an adjunct for complete therapy. With these facts in mind, the hybridization of the salient features of Camoquin or chloroquine with those of Diodoquin or Vioform would be of great interest. Recently,

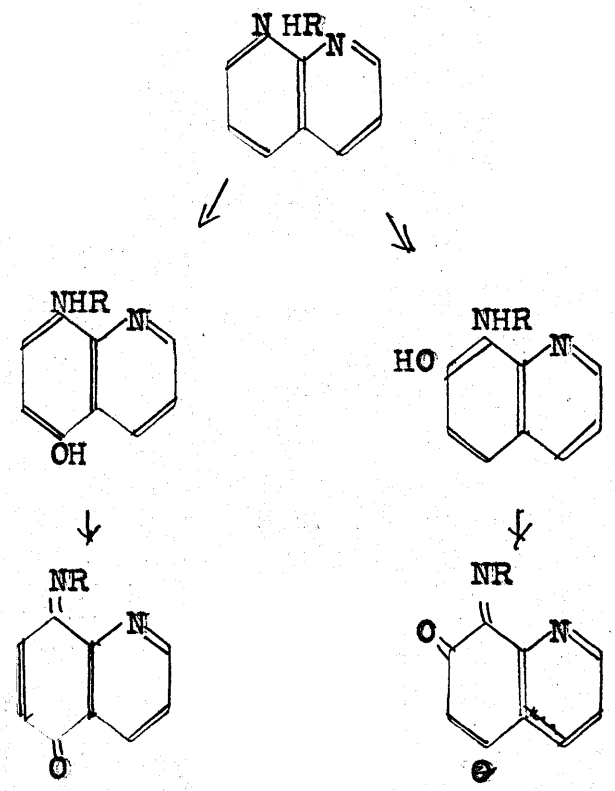
the 7-iodo derivative of chloroquine has been reported to have appreciable amebacidal activity[19].

III. THEORETICAL

Quinolinol Antimalarials

It is generally agreed that no single mechanism accounts for the prophylactic, suppressive, or curative action of all the various antimalarial drugs against the gamut of strains of species of causative parasites in different hosts. An insight into a possible theory which may account for activity of the 8-aminoquinolines and their relatives was deduced from the observation that methemoglobinemia is a common result of the introduction of these drugs into animals. Methemoglobinemia (presence of an oxidized form of oxyhemoglobin in the blood) is also caused by the ingestion of aniline and many of its congeners. The oxidative degradation of aniline is postulated to proceed through the ortho and para hydroxy forms and then to the quinonimines which are the toxic products.

The extensive degradation of plasmodicides when metabolized is well known. Plasmochin has exhibited much greater antimalarial activity in <u>in vivo</u> tests than in <u>in vitro</u> tests, thus suggesting that an active degradation product or process might be the source of activity. 8-Aminoquinolines can form quinonimines similar to those derived from aniline. Only the 4-, 6-, and 8-aminoquinolines of the seven possible isomers were found to have antimalarial

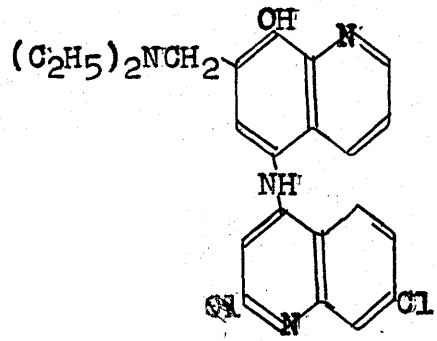


activity. Schönhöfer[3] postulated that the reason for this experimental fact was that only these three aminoquinolines had the structures necessary to form possible quinonimines.

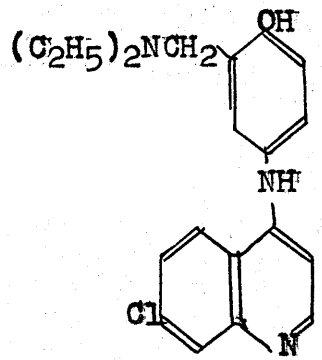
Although there are several anomalies to the Schönhöfer theory, an overwhelming proportion of derivatives show activities which support the theory. Acylation of the aromatic secondary amino groups of 8-aminoquinoline derivatives completely obliterates the activity of the parent. Substituents in the positions vital for quinoidation also diminish activity. Substituents, such as the methoxyl group, which might aid quinoidation increase activity. Therefore, the Schönhöfer theory appears attractive in explaining anti-malarial activity if full cognizance of the limitations of

the theory and the complexity of antimalarial activity is maintained.

Several compounds which were to be synthesized in the present studies possessed systems which would easily lead to quinonimine formation. In addition, all were to contain the Mannich base side chain in order to obtain a satisfactory physiological distribution of the drug through greater solubility. Compound XVI is a close congener of Camoquin, a good suppressive antimalarial.

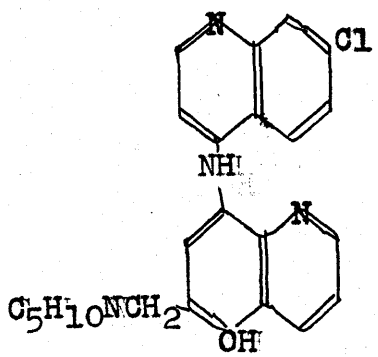


XVI

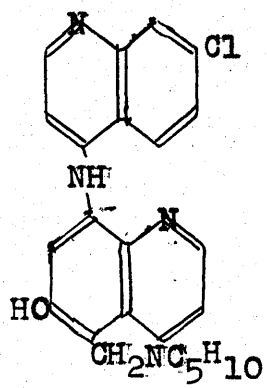


Camoquin

Compound XXVI is a hybrid of the 8-aminoquinoline with the



XXVI

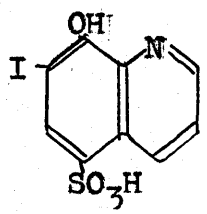


XXXII

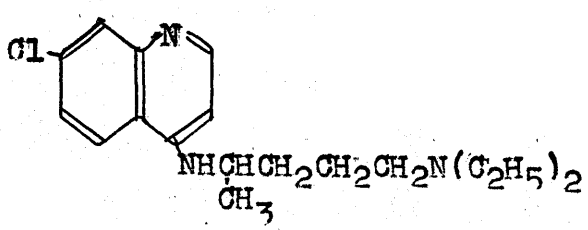
4-aminoquinoline drugs, thus combining potential gametocidal and suppressive activity by the hybridization. Compound XXXII would be similar to XXVI; however the hydroxyl group meta to the quinolylamino group would not be as favorable to facile quinoidation as the situation which the para hydroxyl groups present in compounds XVI and XXVI. A lower activity in compound III would be interesting from the viewpoint of the Schönhöfer theory.

Quinolinol Amebacides

A wide variety of drugs has been used to treat various cases of amebiasis. Examination of these drugs reveals the widespread use of quinoline derivatives and the preference of physicians for them. The amebacidal action of the quinoline drugs is usually attributed to an active halogen atom or perhaps an alkoxyl group together with the overall quinoline structure. Often a solubilizing group is present to enable the drug to reach the site of action. Chiniofon is a good example of an intestinal amebacide. The iodine

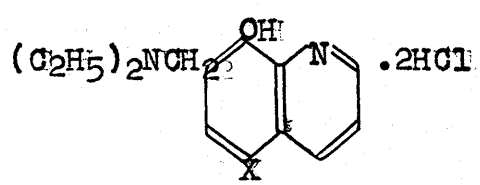


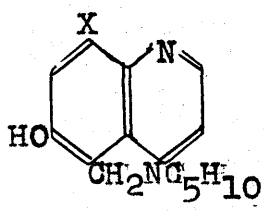
Chiniofon



Chloroquine

atom is undoubtedly the toxicant. The sulfonic acid radical is the solubilizing group. The group of compounds in the present work follow this same pattern by combining a toxicant halogen atom with a solubilizing Mannich side chain, both substituted in the benzenoid ring of quinoline. These compounds are of the following type:

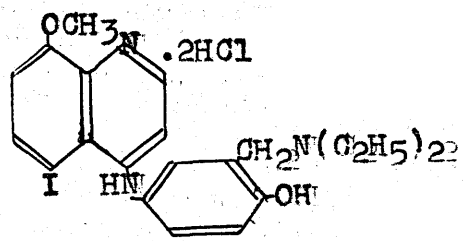




Chloroquine has shown great progress in the chemotherapy of extraintestinal amebiasis and is gradually replacing the toxic emetine. No theory has been postulated for the action of extraintestinal amebacides. Chloroquine, however, fits into the same structural pattern as do the intestinal drugs. The chloro atom is possibly the toxic atom while the noval diamine side chain is the group which assures physiological distribution of the drug. While the foregoing analysis of quinoline amebacides perhaps oversimplifies the actual mode of action of the drugs, such analysis might be valuable in the synthesis of more general, non-toxic amebacides.

A hybridization of chloroquine or Camoquin with Diodoquin or Chiniofon in a structure such as LXXIV might

produce a compound which would be active in both phases of amebiasis.

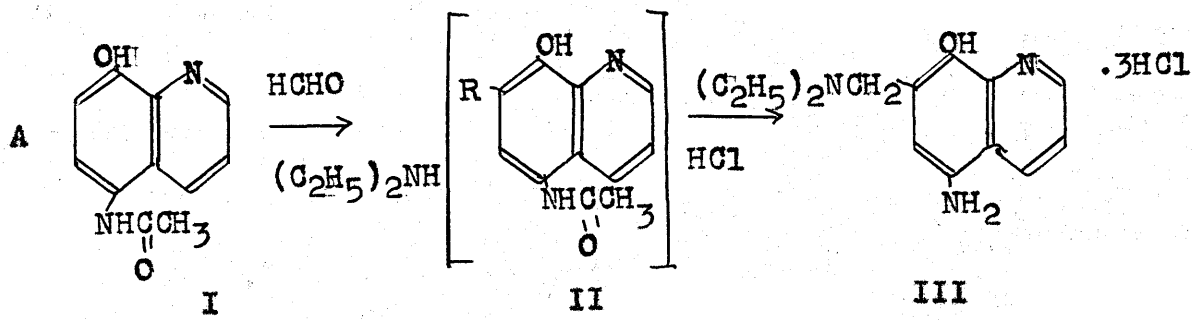


LXXIV

IV. DISCUSSION

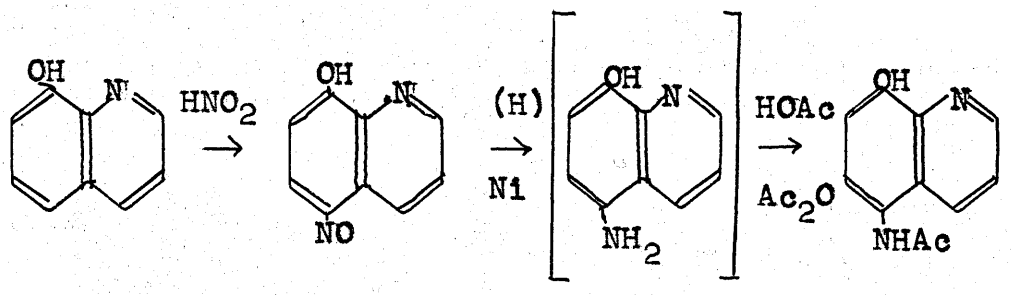
Quinolinol Antimalarials

Source of Activity of Impure 5-Amino-7-diethylaminomethyl-8-quinolinol Trihydrochloride.(III)



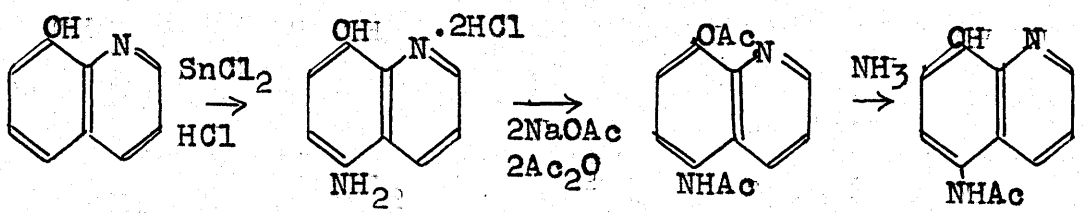
I II III

As stated in the Introduction, an impure sample of III exhibited exceptional antimalarial activity. In the chemical investigation of the source of the activity, it was decided to attempt to prepare for antimalarial testing the compounds actually used as intermediates in the original synthesis and those which might result as by-products. Further, it was decided also to prepare III by a route different from the original, to repeat the original synthesis in order to obtain an impure sample of III as well as a very pure sample of III. The pharmacological comparison of these three samples would be very revealing.

B 

IV V VI I

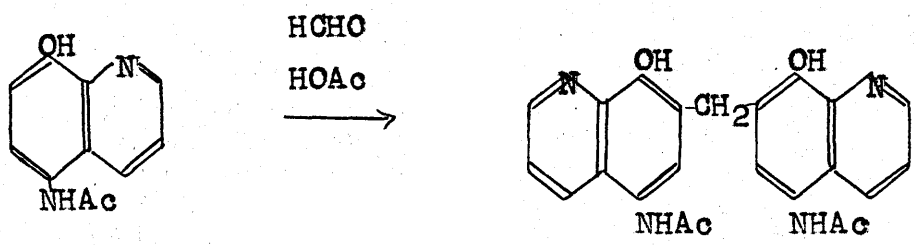
During the preparation of an important intermediate, 5-acetamido-8-quinolinol[20] (I), trouble was encountered in the reduction and subsequent acetylation of 5-nitroso-8-quinolinol[21] (V). Catalytic reduction and concomitant acetylation of V was successful in small quantities as indicated in equation B.

C 

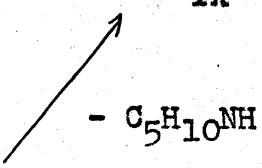
V VII VIII I

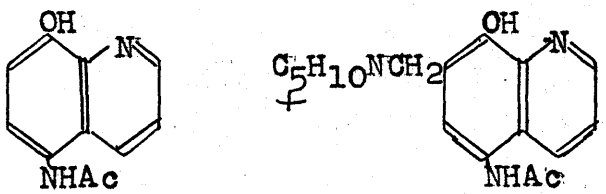
The most consistent productive method of preparing I was reduction of V chemically by the method of von Kostanecki[21b] followed by acetylation in water with two moles of sodium acetate and two moles of acetic anhydride. The O,N-diacetyl derivative (VIII) separated initially from the

acetylation mixture, but the O-acetyl group was removed easily by the addition of concentrated ammonium hydroxide to yield the desired compound (I). I could be purified with difficulty but the crude material was usually sufficiently pure to be used in further reaction.

D 

I IX



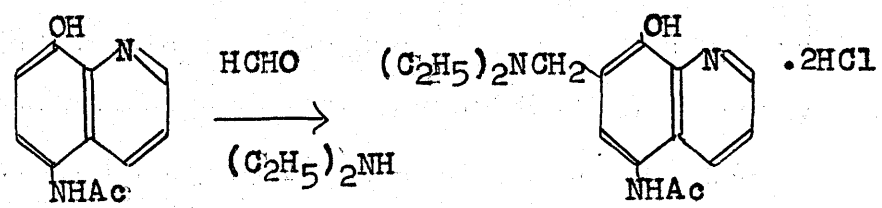
E 

I X

In the course of the original reaction (A), a small amount of insoluble material was recovered which was thought to be either 7,7'-methylene-bis-(5-acetamido-8-quinolinol) (IX) or its deacetylated relative. IX was prepared by two methods: condensation of two moles of I with paraformaldehyde in acetic acid (D) and alkylation of I with 5-acetamido-7-(1-piperidylmethyl)-8-quinolinol (X) (equation E). IX was insoluble in common solvents and decomposed

slowly at high temperatures (above 300°). Attempted deacetylation of IX in concentrated hydrochloric acid resulted in a tan solid precipitating directly from the acid solution after a short refluxing period. This product, which is apparently only the hydrochloride of IX, seemed identical with the hydrochloride made by dissolving IX in a minimum of concentrated hydrochloric acid and precipitating it with acetone. Deacetylation of IX in alkali resulted in dark, decomposition products. Since the bis products were very insoluble and had very little activity (see page 26), work along this line was discontinued.

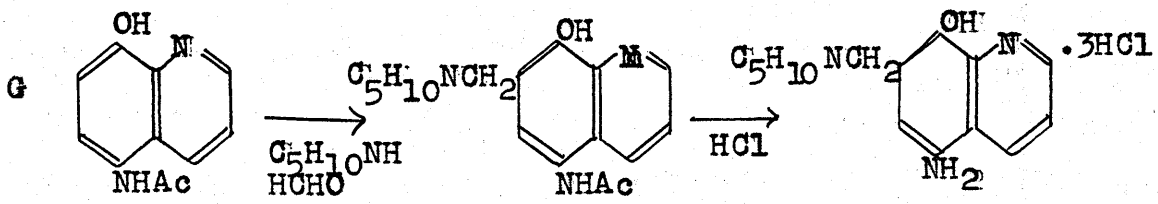
F



I XI

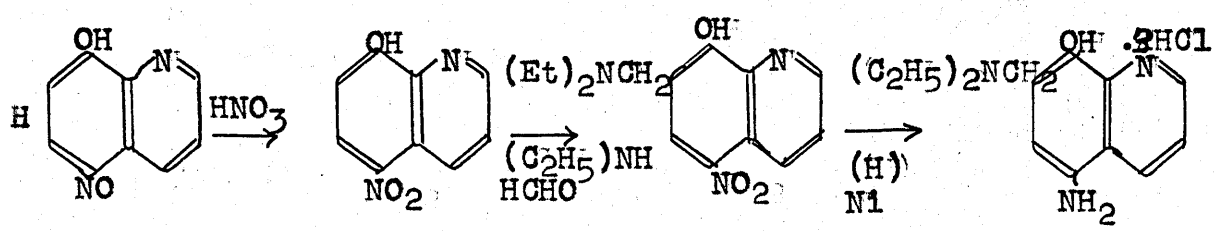
An intermediate which might be present as an impurity in the impure III and thus might account for the antimalarial activity is 5-acetamido-7-diethylaminomethyl-8-quinolinol (XI). XI was not isolated in the original reaction and could not be obtained in a crystalline state but its dihydrochloride was crystallized with difficulty. The piperidylmethyl (X) analogue was isolated very easily as the free base (Equation G). However, both of these Mannich

bases were inactive pharmacologically.



I X XII

An impure sample (XIIa) of 5-amino-7-(1-piperidyl-methyl)-8-quinolinol trihydrochloride (XII) was submitted for antimalarial testing along with a purified sample (XIIb). The two samples had similar activities (page 26). This piperidyl compound should be similar, pharmacologically, to the diethylamine analogue (III)--the product which inspired these studies.



V XIII XIV IIIa

As an intermediate in an alternate synthesis of III, 5-nitro-8-quinolinol[21b,22] (XIII) was prepared by oxidation of V with nitric acid. 7-Diethylaminomethyl-5-nitro-8-

quinolinol[a] (XIV) was then obtained in a standard Mannich reaction and reduced with freshly prepared Raney nickel catalyst in glacial acetic acid. Air must be carefully kept from the free base to keep oxidation at a minimum. III made by this alternate route was designated IIIa for comparison purposes.

Finally, reaction A was repeated to obtain an impure sample of III (IIIb) and a carefully purified sample (IIIc) of the same compound. Pharmacological comparison of these three samples (IIIa, b, and c) indicated the same order of activity for each. Therefore, the conclusion was reached that the activity is inherent in the compound itself, and, further, as admitted by the pharmacologist, the apparent "decrease in activity" may actually be attributable to vagaries in the test method.

---

a Later, it was learned that XIV had been prepared earlier as the monohydrochloride (m.p. 204-205°)[23] for another purpose by Dr. W. F. Holcomb of Parke, Davis & Co.

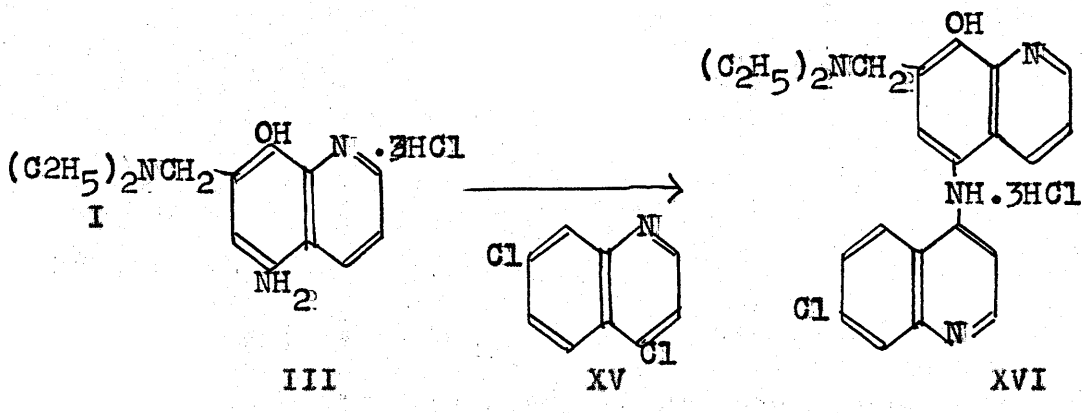
Antimalarial activities

Sample	LC Q	Sample	LC Q
I	<0.075	X	<0.075
IIIa	0.45	VIII	<0.075
IIIb	0.61	XI	<0.075
IIIc	0.53	XIIa	0.28
IX.2HCl	<0.14	XIIb	0.28
IX	<0.15	XIV	<0.3

Original impure III 1.3

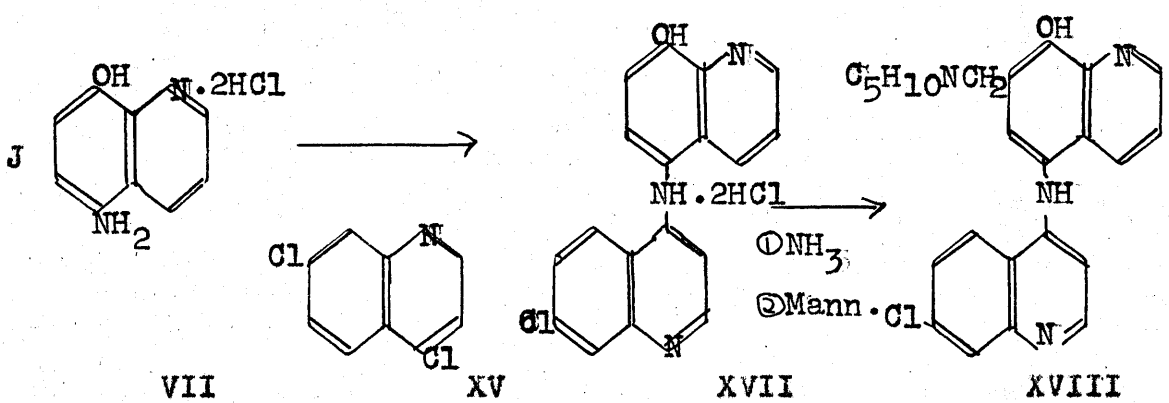
The antimalarial testing was carried out by Dr. Paul C. Thompson of Parke, Davis & Co. The numbers are quinine equivalents as determined in malaria caused by Plasmodium lophurae induced in the chick. The excellent agreement of effectiveness by III (samples a, b and c) indicates that the compound (III) is about half as active as quinine in the test. The conclusion that the original, unusual activity is anomalous is confirmed further by the identical activities of the analogue XII (samples a and b).

5-(7-Chloro-4-quinolylamino)-7-(1-piperidylmethyl)-8-quinolinol (XVIII).



I III XV XVI

One of the prime objects of this investigation which has already been discussed was the synthesis of XVI, a quinoline analogue of the well known Camoquin. Former attempts[1] to prepare XVI by the reaction reproduced above (I) were unsuccessful. The failure of this approach was confirmed; however, an alternate method (J), consisting of synthesis of the diquinolylamine skeleton and then use of the Mannich reaction proved satisfactory.

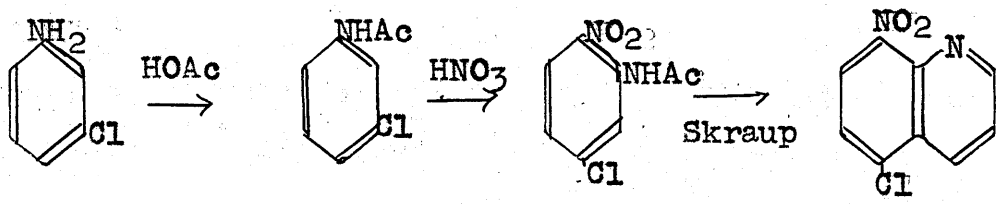


VII XV XVII XVIII

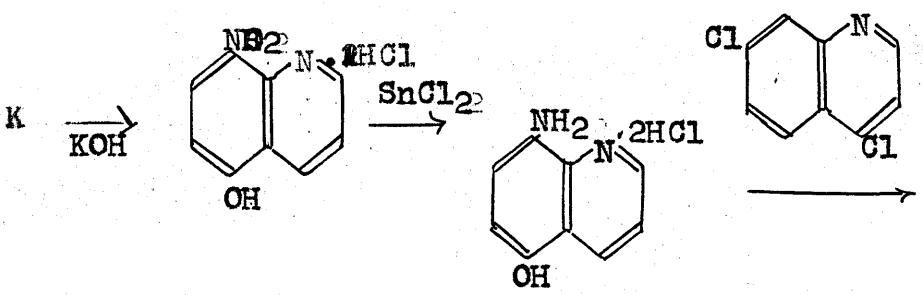
VII was condensed easily with 4,7-dichloroquinoline (XV) to yield 5-(7-chloro-4-quinolylamino)-8-quinolinol dihydrochloride hemihydrate (XVII). While XVII would not form a Mannich base under the experimental conditions commonly used, its free base reacted readily in alcohol; more difficultly in glacial acetic acid. The yields are excellent if the starting material (i.e. the base of XVII) is pure. XVIII is a white, crystalline compound which is soluble in dilute hydrochloric acid and insoluble in dilute sodium hydroxide solution. The piperidylmethyl derivative was formed because it is usually more easily crystallized than the diethylaminomethyl Mannich base. The latter compound should be easily prepared in a similar manner.

XVIII was found to have a quinine equivalent of 3.2 in avian malaria. It also was quite non-toxic since it was better tolerated in the chick than Camoquin. Thus XVIII has a relatively high therapeutic index.

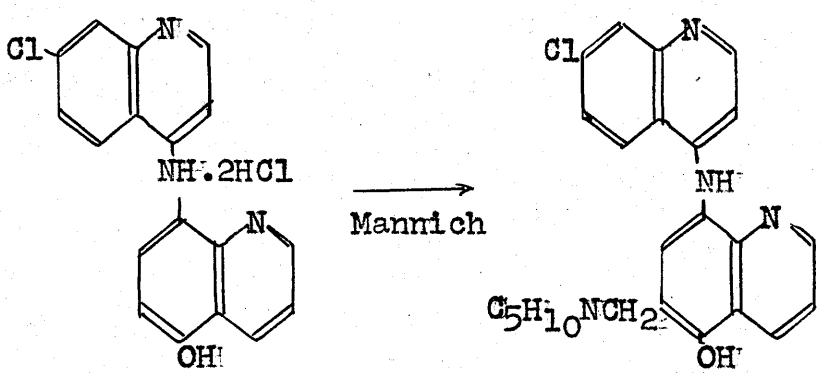
8-(7-Chloro-4-quinolylamino)-6-(1-piperidylmethyl)-5-quinolinol (XXVI).



XIX XX XXI XXII



XXIII XXIV XV



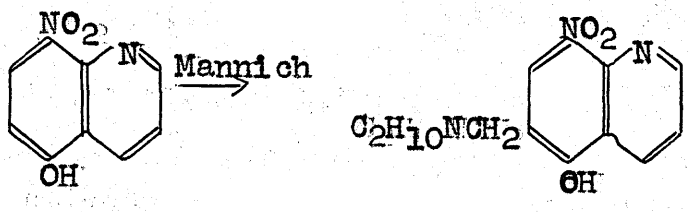
XXV XXVI

The preparation of XXVI was carried out in order to obtain a position isomer of XVIII which would also have structural features necessary to satisfy the requirements of the Schönhöfer theory. XXVI might also be regarded as a hybrid of the 4-amino and 8-amino quinoline antimalarials.

8-Nitro-5-quinolinol (XXIII), an important intermediate in this synthesis, was prepared with several modifications according to the instructions of Fuson et al[24]. In the preparation of 2-nitro-5-chloroacetanilide (XXI), the nitration mixture must be allowed to come to room temperature slowly with stirring in order to circumvent an explosion.

The Skraup reaction on 2-nitro-5-chloroaniline has been the method of choice for the preparation of 5-chloro-8-nitro-quinoline (XXII). Neither the original method of Fourneaou[25] nor a modification of Lutz et al[26] proved satisfactory however. A fine solution was found by the use of the Manske modification[27] of the Skraup reaction which employs an acetanilide (XXI) as starting material. The yields are consistantly 60-70 per cent if the procedure outlined in the Experimental section is followed carefully.

The hydrolysis of XXII was carried out in one step with alcoholic potassium hydroxide. This reaction did not prove applicable to quantities of over two grams of XXII.

L 

XXIII XXVII

The Mannich reaction was carried out with XXIII as starting material. The preparation is very tedious due to the extremely low solubility of XXIII in ethanol. XXVII was thought to be a potential amebacide, aside from its value as an intermediate.

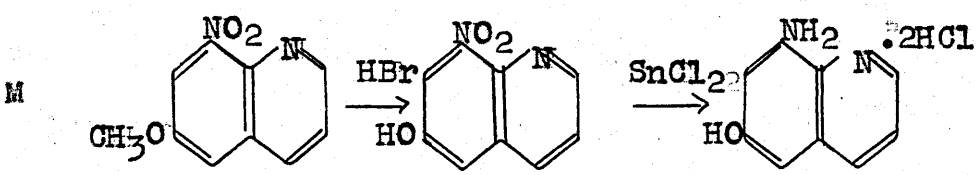
XXIII was reduced with stannous chloride and concentrated hydrochloric acid in essentially the same manner as VI. The yield of 8-amino-5-quinolinol dihydrochloride (XXIV) was 70-75 per cent. XXIV was previously reported as the sulfate prepared by an electrolytic reduction[20a,28]. The various aminoquinolinolhydrochlorides used in this work were extremely hard to purify due to extensive oxidation and were often used in subsequent reactions in the crude form.

The condensation of XXIV with XV was accomplished easily to produce a yellow, cottony compound which was more soluble in ethanol than its isomer (XVIII).

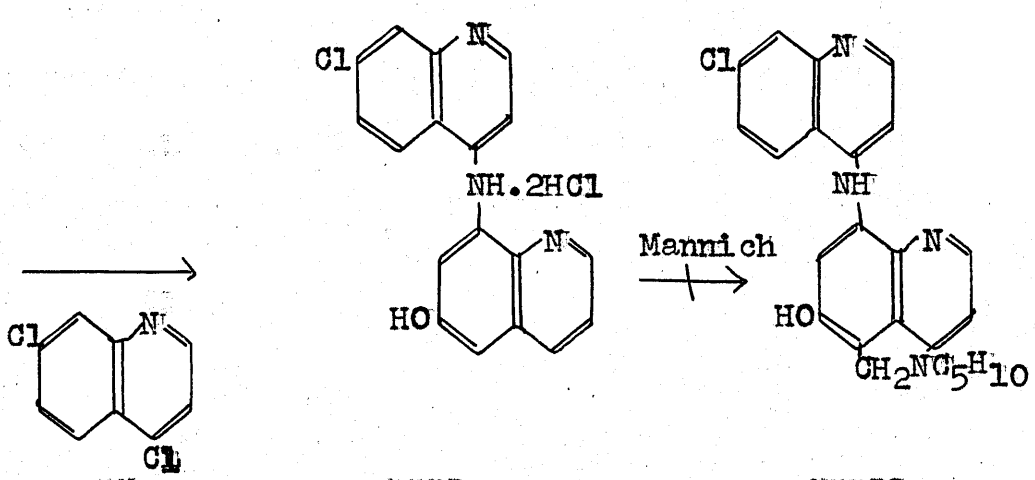
Although the free base of 5-(7-chloro-4-quinolylamino)-8-quinolinol dihydrochloride hemihydrate (XXV) could not be isolated, the Mannich reaction with XXV and three moles of piperidine was successful. The beautiful

yellow crystals are soluble in dilute hydrochloric acid and insoluble in dilute sodium hydroxide solution. XXVI has a quinine equivalent of 0.15 in avian malaria. These results are rather disappointing; however, the fact that some antimalarial activity is present is interesting.

Attempted Preparation of 8-(7-Chloro-4-quinolylamino)-5-(1-piperidylmethyl)-6-quinolinol (XXXII).



XXVIII XXIX XXX



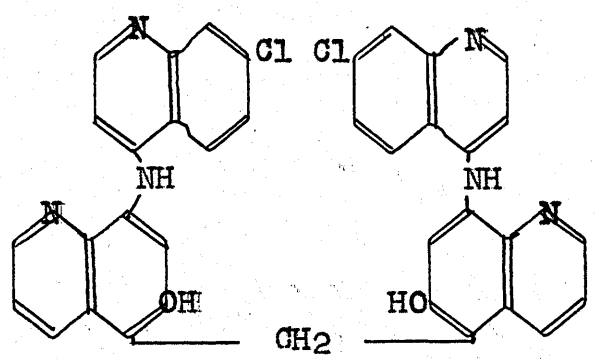
XV XXXI XXXII

An attempt was made to prepare XXXII, a third isomer of XXVI and XVIII. This compound would be interesting with respect to its pharmacological activity. It does

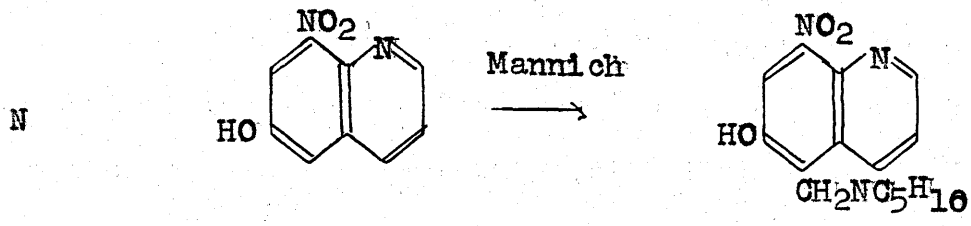
not fulfill the Schönhöfer precepts as completely as its other two isomers because of the meta position of the hydroxyl group in relation to the 8-amino group. Such position would prevent the facile quinoidation which is possible in XXIII and XXVI.

8-nitro-6-quinolinol (XXIX)[29], obtained by demethylation of the commercially available 6-methoxy-8-nitroquinoline, was reduced in the standard method with stannous chloride and concentrated hydrochloric acid to produce 8-amino-6-quinolinol dihydrochloride (XXX). The base of XXX was previously prepared by reduction of the proper coupled diazo compound by Matheus[30] who also described formation of the hydrochloride but neglected to give a melting point.

The condensation of XXX with XV was readily carried out but repeated attempts to obtain the Mannich base of XXXI, even employing high dilution technique, resulted in an insoluble, yellow powder which decomposed at high temperatures and is probably the bis compound (XXXIII).



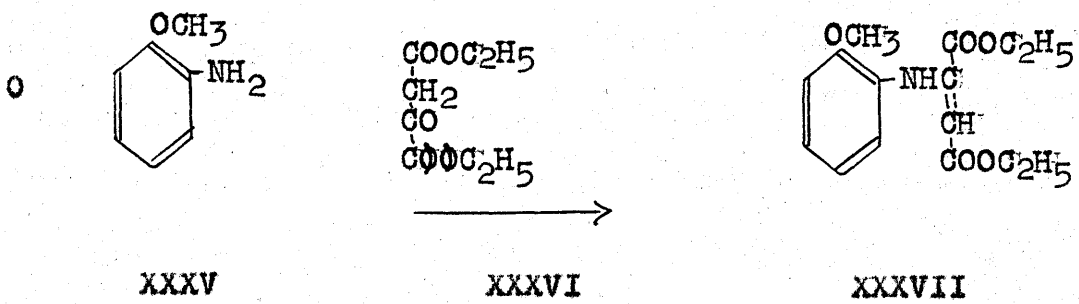
XXXIII



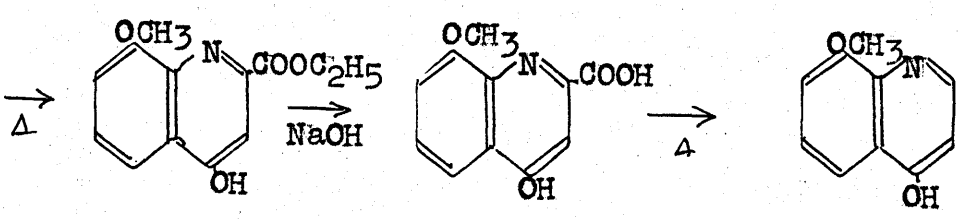
XXIX XXXIV

The Mannich reaction was carried out with XXIX in the standard manner to obtain XXXIV, an congener of two compounds previously prepared (XIV and XXVII). Perhaps later work will show that it can be employed in the preparation of a type XXXII compound.

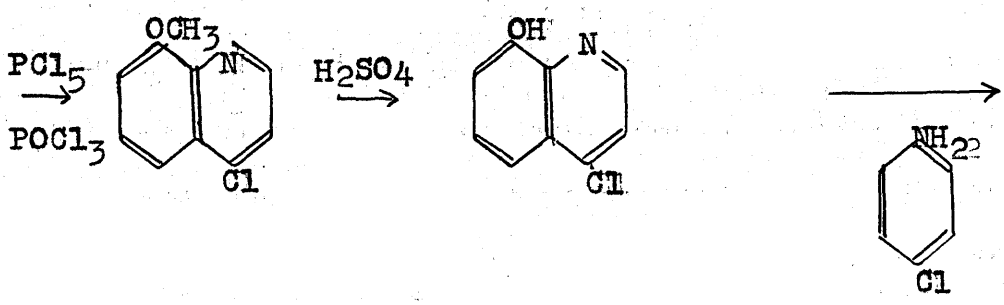
4-(4-Chloroanilino)-7-(1-piperidylmethyl)-8-quinolinol (XLV).



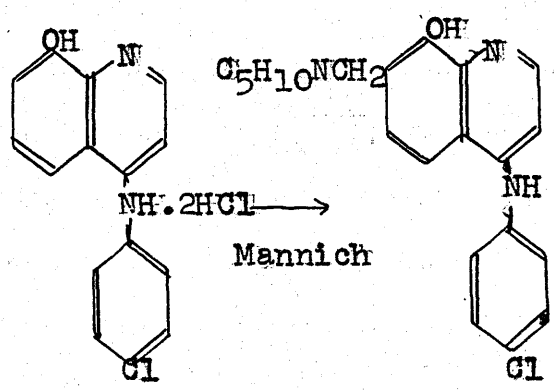
XXXV XXXVI XXXVII



XXXVIII XXXIX XL



XLI XLII XLIII



XLIV XLV

XVL is an isomer of Camoquin which does not possess a system which would facilitate quinonimine formation suggested by the Schönhöfer theory as readily as several of the preceding compounds (III, XVIII, XXVI); however it is interesting in its own right since it is a position isomer of a Camoquin homologue.

4-Chloro-8-methoxyquinoline[31] (XLI) has been made by the ethoxymethylenemalonic ester (EMME) synthesis using o-anisidine as starting material. Since the sodium salt of oxalacetic ester (XXXVI) is readily available, the modified

Conrad-Limpach synthesis[32] was utilized to prepare the desired intermediate (XLI). It was found that the overall yield was much lower than that reported by Lauer who used the "EMME" method.

XLI was hydrolyzed with 60 per cent sulfuric acid[33] to obtain 4-chloro-8-quinolinol (XLII) which is, contrary to expectations, only slightly soluble in 5 per cent sodium hydroxide solution.

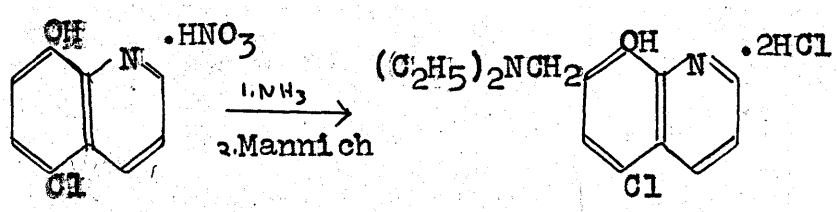
p-Chloroaniline (XLIII) was condensed with XLII in the standard manner by refluxing in ethanol. The product, 4-(4-chloroanilino)-8-quinolinol hydrochloride (XLIV), is slightly soluble in water. It is quite soluble in ethanol but isopropanol was found to be preferable for recrystallization. The Mannich base of XLIV was prepared by using two moles of piperidine to obtain the desired product, XLV.

Quinolinol Amebacides

The Mannich bases of several halogen substituted quinolinols were prepared in accordance with the pattern suggested previously, i.e., that such compounds would contain a solubilizing group substituted in the halogenated quinolinol skeleton which has been proved effective in amebiasis (Vioform, Chiniofon, etc.).

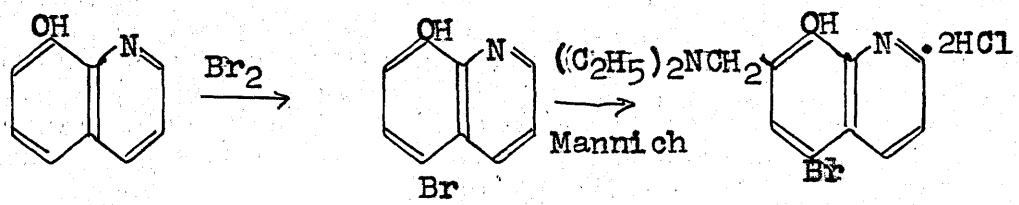
5-Halo-8-quinolinols

P



XLVI XLVII

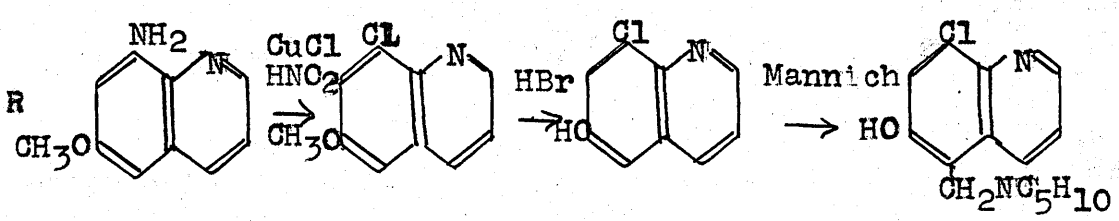
Q



IV XLVIII XLIX

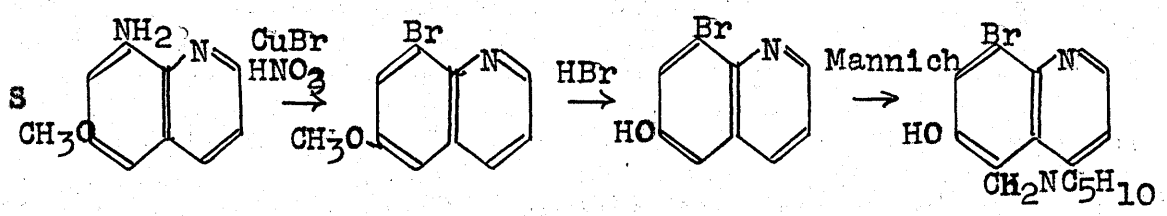
The 5-chloro- (XLVII) and 5-bromo-quinolinol (XLIX) Mannich bases were synthesized; however the 5-iodo congener could not be isolated. After several attempts at both iodinating 7-piperidylmethyl-8-quinolinol[34] and using the Mannich reaction with 5-iodo-8-quinolinol[35], the conclusion was reached that this most interesting member of the series was too hygroscopic to be isolated in a crystalline state. (The fluoro analogue has also been prepared by Dr. Arthur Helin of the Chemistry Department.) In preliminary amebacidal tests at the Parke, Davis & Co. laboratories, XLVII and XLIX have exhibited fairly good activity.

8-Halo-6-quinolinols



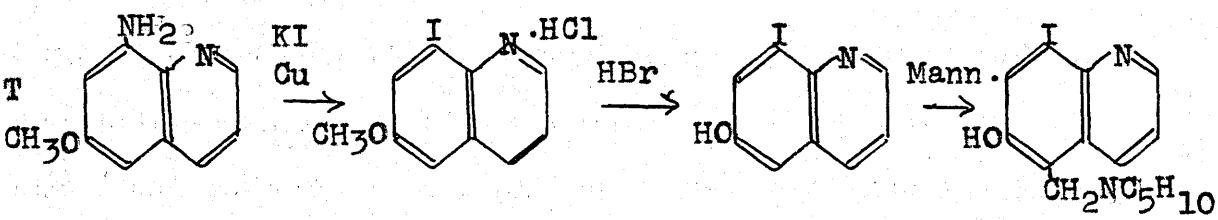
L LI LII LIII

8-Chloro-6-methoxyquinoline (LI) was prepared by a Sandmeyer reaction on 8-amino-6-methoxyquinoline (L) as described by Price et al[36]. LI was demethylated with 48 per cent hydrobromic acid to yield the previously unreported 8-chloro-6-quinolinol (LII). The 8-halo-6-quinolinols have very high melting points as compared to the 5-halo-8-quinolinols and 6-chloro-8-quinolinol. The Mannich reaction using LII as starting material produced 8-chloro-5-(1-piperidylmethyl)-6-quinolinol dihydrochloride (LIII) analyzed as the sesquihydrate. The Mannich group was assumed to enter the 5 position rather than the 7 position because of the evidence of previous similar instances[37] and the predominance of the resonance form indicated in LII.



L LIV LV LVI

Since the Sandmeyer procedure outlined by Berkenheim and Antik[38] for the preparation of 8-bromo-6-methoxyquinoline (LIV) yielded poor results, a procedure similar to the preparation of LI was used. The hydrochloride of LIV was obtained in fair yield (49%) and was used as such in the subsequent demethylation. 8-Bromo-5-piperidylmethyl-6-quinolinol (LVI) was prepared by the Mannich reaction as stable, brown plates.

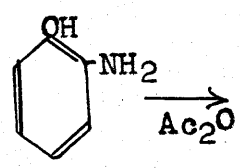


L LVII LVIII LIX

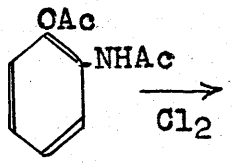
Although 8-iodo-6-methoxyquinoline (LVII) was reported by Price *et al*[36], only a suggestion of the method used was included in his paper. The details of the Gattermann reaction were clarified to obtain LVII in 25 per cent yield. 8-Iodo-6-quinolinol (LVIII) was purified by vacuum sublimation at 0.2-0.3 mm. as was LV. 8-Iodo-5-piperidylmethyl-6-quinolinol (LIX) was a beautiful, crystalline compound which, contrarywise to its 5-iodo-8-quinolinol isomer, darkened only slightly on prolonged exposure to air.

Miscellaneous Haloquinolinols

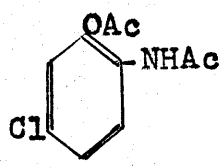
U



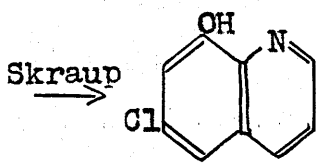
LX



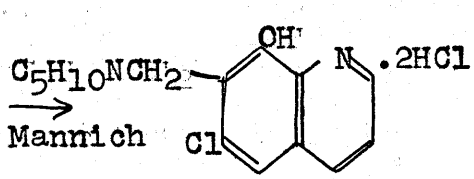
LXI



LXII



LXIII



LXIV

In the acetylation of o-aminophenol (LX), results different from those previously reported in the literature were obtained. Acetylation by refluxing in an excess of acetic anhydride for either one-half hour, a method by which Theilacker[39] obtained LXI, or twelve hours produced a compound which melted at 78-80° and which evidently is the O-acetyl derivative. Bamberger[40] reported that acetylation of LX in a mixture of acetic anhydride and ethyl acetate produced the o,N-diacetyl derivative (LXI); however this reaction yielded a compound which melted at 200-202° and

which apparently is the N-acetyl derivative[41]. The desired compound (LXI) was finally obtained by the use of acetic anhydride and LX in pyridine solution as suggested by LeRosen and Smith[41].

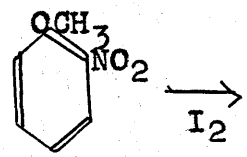
It was found that 6-chloro-8-quinolinol (LXIII)[42] was obtained most satisfactorily from the Skraup reaction mixture by vacuum sublimation. 6-Chloro-7-piperidylmethyl-8-quinolinol dihydrochloride (LXIV) was obtained from the Mannich reaction as a hydrate. Note should be made that fractional amounts of water are often indicated by the analytical data. This fact is probably because drying over phosphorous pentoxide under low vacuum abstracts a portion of the water held by the compound in question. The presence of a hydrate is often difficult to predict in advance. Since the free base of LXIV was insoluble in 5 per cent sodium hydroxide solution, it was assumed that the Mannich group had entered the 7 position[43].

Attempts to brominate and iodinate LX resulted in mixtures of inconclusive products. Time prevented further work along this line.

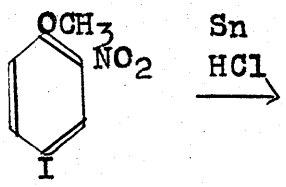
4-Substituted Aminoquinolines

In view of the recent recognition of the extra-intestinal amebacidal value of the 4-aminoquinolines[4], an attempt to synthesize a hybrid of Diodoquin and Camoquin

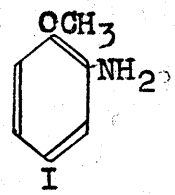
was initiated. Such a compound would be of interest for testing in both phases of amebiasis.

V 

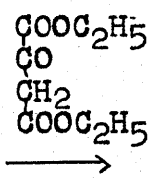
LXV



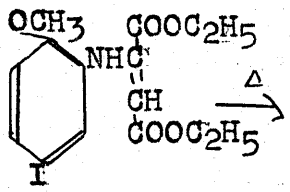
LXVI



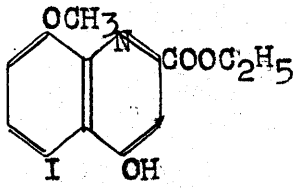
LXVII



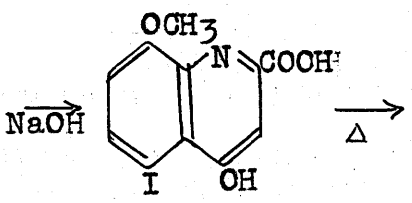
XXXVI



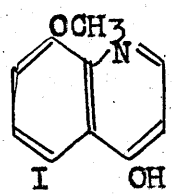
LXVIII



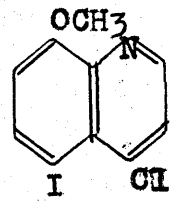
LXIX



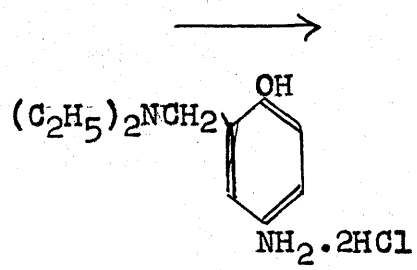
LXX



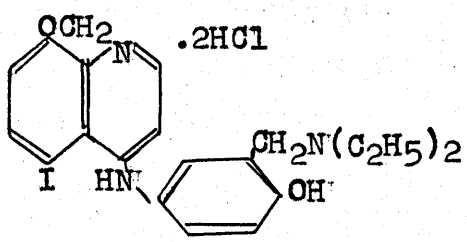
LXXI



LXXII



LXXIII



LXXIV

The problem of preparing the proper 4-chloroquinoline was attacked from two directions. Iodination of XLII (p. 35) with iodine chloride produced a high melting, insoluble solid which could not be condensed with the Camoquin side chain (LXXIII). The alternate route (V) was more successful.

The reduction of 2-nitro-4-iodoanisole[44] (LXVI) was successful with tin and hydrochloric acid but extraction of the product with ether was extremely tedious due to the presence of voluminous tin salts.

The oxalacetic ester synthesis was used to form the desired 4-quinolinol. Some trouble was encountered in obtaining the free ester from the commercially available sodioethyloxalacetate due to the extensive decomposition of the ester upon heating. Distillation through a very short column at low pressure was necessary to obviate the difficulty[45].

Two equally satisfactory methods were used to form the acrylate (LXVIII). Either the ester (XXXVI) was condensed with the amine (LXVII) or the sodium salt of the ester was condensed with the hydrochloride of the amine in the manner suggested by Lisk and Stacy.[46]

The cyclization of the acrylate was found to proceed to completion in 35 to 45 minutes in refluxing diphenyl ether. The use of mineral oil as diluent is not

advisable because of extensive decomposition of the iodine compound. This abnormally long heating period for ring closure is undoubtedly due to the bulky nature of the 5-iodo substituent.

Decarboxylation of LXX at high temperatures yielded an insoluble, infusible residue which is probably caused by the loss of the iodine atom. The decarboxylation, however, proceeded without decomposition at 220-230° but some unreacted acid remained. It was separated by prolonged stirring with sodium carbonate solution. 5-Iodo-8-methoxy-4-quinolinol (LXXI) has an abnormally low melting point since a hydrate is formed.

4-Chloro-5-iodo-8-methoxyquinoline (LXXII) was prepared by the action of phosphorous pentachloride and phosphorous oxychloride on LXXI. The crude product obtained from benzene extraction of the neutralized reaction mixture is best purified by vacuum sublimation at as low a temperature as possible. Sublimation at high temperatures produces a tarry sublimate. The yields are very low but are much higher than those obtained by using phosphorous oxychloride alone.

LXXII was condensed with the Camoquin side chain (LXXIII) in excellent yields; however the resulting product (LXXIV) could not be easily purified. LXXIV recrystallized nicely from isopropanol but upon filtration the crystals

proved to be very hygroscopic. No solvent was found which was satisfactory for recrystallization. A small amount was finally reprecipitated from isopropanol solution with acetone to yield a stable hydrate form.

LXXIV could not be demethylated with 48 per cent hydrobromic acid to give a desired 8-quinolinol. A dark reaction mixture resulted from which no product could be isolated. However, LXXIV itself may prove to be just as interesting since many similar compounds (Atabrine) are demethylated in vivo.

A suggestion for future work toward the synthesis of the demethylated relative of LXXIV is the initial demethylation of LXII, followed by condensation of the resulting 4-chloroquinolinol with the Camoquin side chain (LXXIII) to produce the desired product. Such a course of action would immediately form the dihydrochloride which is evidently more stable than the free base.

It should also be noted that although the compounds reported have been divided into two groups, antimalarials and amebacides, for purposes of discussion, all the compounds possess interesting possibilities in both directions, a fact which may be aptly illustrated by LXXIV and XLV. These compounds have structures which may have potentialities against either parasite. Fragmentary reports on the compounds tested at the time of writing have corroborated this reasoning.

Although the Mannich reaction is dominant throughout the experimental part of this paper, no effort has been made to discuss it in detail since excellent review articles[52] are available on the subject. Recently, the first article of a series on the mechanism of the Mannich reaction appeared in the literature.[53]

V. EXPERIMENTAL[a]

Quinolinol Antimalarials

5-Nitroso-8-quinolinol (V)[21b].---Thirty-six grams (0.25 mole) of 8-quinolinol (IV) was dissolved in a mixture of 45 ml. of concentrated hydrochloric acid and 45 ml. of distilled water. The solution was cooled to 8° and a saturated solution of 18 g. (0.25 mole) of sodium nitrite in water was added with efficient stirring over a two hour period. The mixture was then tested with starch-potassium iodide paper to verify an excess of nitrous acid. The thick yellow solid was collected on a Buchner funnel, washed with water, and pressed with a rubber dam to yield 47.5 g. (91%) of the hydrochloride of V.

A solution of 20 g. of sodium hydroxide in 300 ml. of water was added to 47 g. (0.22 mole) of the hydrochloride of V dissolved in a minimum of water. The resulting red solution was treated with Norite, filtered, and made acidic with dilute acetic acid to yield 37.3 g. (95%) of yellow V; m.p. 240°-245° (dec.) (reported m.p. 220-245°[21b]).

5-Amino-8-quinolinol Dihydrochloride (VII).---Two hundred and eleven grams (1 mole) of the hydrochloride of V

---

a All melting points and boiling points are uncorrected; all carbon, hydrogen analyses are by Mr. Charles Beazley, Skokie, Illinois.

was slowly added to an agitated solution of 500 g. of crystalline stannous chloride in 600 ml. of concentrated hydrochloric acid at a rate which kept the temperature below 20°. The mixture was then heated at 60° for six hours. The red tin salt was separated by filtration, washed with concentrated hydrochloric acid, and dissolved in 2½ l. of hot water. Hydrogen sulfide was passed into the aqueous solution until no further precipitate was formed. The solution was filtered through a sintered-glass filter and concentrated in vacuo on the steam bath as rapidly as possible to yield 100.3 g. (54%) of beautiful yellow crystals; m.p. 240-245° (dec.) (reported m.p. 245°)[21b].

5-Acetamido-8-quinolinol (I) Method A.---Eight and seven-tenths grams (0.05 mole) of V was suspended in glacial acetic acid along with 9.5 ml. of acetic anhydride and 0.1 g. of Adams catalyst. During the subsequent, low-pressure hydrogenation, the theoretical quantity of hydrogen was absorbed and heat was evolved. The clear solution was refluxed for six hours. The spend catalyst was removed from the warm solution by filtration. After standing overnight, 0.6 g. of unidentified yellow crystals separated; m.p. 264°. The filtrate was concentrated until it began to bump badly. Trituration of the concentrated solution with ammonium hydroxide produced 5.4 g. (54%) of grey solid; m.p. 208°. The product may be purified by recrystallization from

ethanol; m.p. 219-220° (reported m.p. 221-222°)[20].

Method B.---A solution of 15 g. (0.06 mole) of VII in as little water as possible was heated to 50° with efficient stirring. A solution of 17.4 g. (0.12 mole) of crystalline sodium acetate in water was quickly added together with 13.8 g. (0.12 mole) of acetic anhydride. After heating at 50-55° for two hours, a yellow mass separated. The cooled solid was separated by filtration; m.p. 207-208°. The diacetylated derivative (VIII) was triturated with ammonium hydroxide to form 12.0 g. (92%) of the desired product; m.p. 214-215°.

7,7'-Methylene-bis-(5-acetamido)-8-quinolinol (IX)

Method A.---A solution of 9.0 g. (0.044 mole) of I and 0.67 g. (0.022 mole) of paraformaldehyde in glacial acetic acid was refluxed for two hours. After separation by filtration and washing with acetone, 8.0 g. (87%) of tan solid was recovered; this material was extremely insoluble in common organic solvents and decomposed slowly above 275°.

Method B.---A suspension of 3.0 g. (0.01 mole) of 5-acetamido-7-(1-piperidylmethyl)-8-quinolinol (X) and 2.0 g. (0.01 mole) of I in 50 ml. of methanol-ethanol mixture was heated on the steam bath until the solvent was nearly gone. Glacial acetic acid was added to the residue. The clear solution was heated at reflux for five and one-half hours. The addition of 35 ml. of water separated a product which

possessed properties similar to those of the solid obtained in Method A; 2.0 g. (48%), m.p. 300° (gradual dec.). The solid was soluble in dilute sodium hydroxide solution. Dilution with water caused partial precipitation but a pellet of sodium hydroxide cleared the solution once again. Excess acetic acid forced the product from solution. Purification was accomplished by recrystallization from a large volume of quinoline.

Anal. Calcd. for $C_{23}H_{20}N_4O_4$: C, 66.33; H, 4.84. Found: C, 66.33; H, 4.87.

5-Acetamido-7-diethylaminomethyl-8-quinolinol Dihydrochloride (XI).---A solution of 20.0 g. (0.1 mole) of I in 1 l. of absolute ethanol along with 21.5 ml. (0.21 mole) of diethylamine and 3 g. (0.1 mole) of paraformaldehyde was refluxed for one and one-half hours. A small amount of bis product (IX) was separated by filtration. The volatile materials were evaporated in vacuo until a thick sirup remained. Addition of ethyl ether forced a brown sirup from solution. Decantation of the ether and trituration of the sirup with acetone with vigorous stirring by hand produced 26 g. (74%) of yellow solid; m.p. 198° (dec.). The product can be recrystallized from ethanol with difficulty; m.p. 203-204° (dec.)

Anal. Calcd. for $C_{16}H_{21}N_3O_3.2HCl$: C, 53.34; H, 6.43. Found: C, 53.34; H, 6.56.

5-Acetamido-7-(1-piperidylmethyl)-8-quinolinol (X).---A solution of 7.8 g. (0.039 mole) of I, 1.3 g. (0.041 mole) of paraformaldehyde, and 9.0 ml. of piperidine in 150 ml. of ethanol was refluxed for one hour. The condenser was removed and the solution allowed to boil off to a volume of 40-50 ml. Some insoluble material (IX) was separated by filtration. After standing for two hours, the solution yielded 4.0 g. of brown solid. The filtrate was evaporated to dryness and the residue triturated with isopropanol to yield 6.6 g. The total yield after washing the combined portions of solid with petroleum ether was 10.6 g. (92%); m.p. 171° (dec.). White crystals were obtained by recrystallization from an ethanol-isopropanol mixture; m.p. 197-198° (dec.).

Anal. Calcd. for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07. Found: C, 68.05; H, 6.94.

5-Amino-7-(1-piperidylmethyl)-8-quinolinol Trihydrochloride (XII).---A solution of 9.2 g. (0.031 mole) of X in an excess of alcoholic hydrogen chloride was heated at reflux until yellow crystals separated. The product was removed by filtration and washed with acetone to yield 11.2 g. (98%) of crystals; m.p. 234° (dec.). After several recrystallizations from absolute ethanol, a melting point of 236-237° (dec.) was attained.

Anal. Calcd. for $C_{15}H_{19}N_3O.3HCl$: C, 49.13; H, 6.05. Found: C, 49.50; H, 6.10.

5-Nitro-8-quinolinol (XIII).--- A suspension of 117 g. (0.56 mole) of the hydrochloride of V in water was dissolved in a solution of 50 g. of sodium hydroxide in 700 ml. of water. V was formed by acidification with dilute acetic acid.

The moist V was added to 400 ml. of nitric acid (sp. g. 1.38) with efficient stirring and cooling below 50°. Stirring was continued for one hour. Addition of 20% sodium hydroxide until the mixture was basic formed a thick, red sodium salt. Acidifying with acetic acid, filtration, and washing with water produced 100 g. (94%) of yellow solid; m.p. 170-171°. The product was purified by vacuum sublimation to yield yellow crystals; m.p. 172-173° (reported m.p. 173°)[22].

7-Diethylaminomethyl-5-nitro-8-quinolinol (XLV).--- A solution of 5. g. (0.026 mole) of XIII, 0.8 g. (0.026 mole) of paraformaldehyde, and 3 ml. (0.029 mole) of diethylamine in 400 ml. of absolute ethanol was refluxed for one and one-half hours. Cooling produced 6.0 g. (83%) of yellow crystals m.p. 205-206° (dec.). Concentration of the filtrate produced 1.0 g. of crystals. The total yield is quantitative. Recrystallization from butanol produced no rise in melting point.

Anal. Calcd. for $C_{14}H_{17}N_3O_3$: C, 61.07; h, 6.23. Found: C, 61.16; H, 6.25.

5-Amino-7-diethylaminomethyl-8-quinolinol Trihydrochloride (III) Method A[1].---A solution of 9 g. (0.045 mole) of I in 400 ml. of absolute ethanol was refluxed for three hours with 5.2 ml. (0.05 mole) of diethylamine and 1.5 g. (0.05 mole) of paraformaldehyde. One hundred milliliters of alcoholic hydrogen chloride was added to the solution and the reflux period extended for one hour. A small amount of bix product (IX.2HCl) was separated from the solution. The volume was reduced on the steam bath to about 50 ml. Cooling produced 10 g. (64%) of red solid; m.p. 209-211° (dec.) (IIIb). The product can be purified by several recrystallizations from methanol; m.p. 218-219° (dec.) (IIIc).

Anal. Calcd. for $C_{14}H_{19}N_3O.3HCl$: C, 47.40; H, 6.25. Found: C, 47.64; H, 6.61.

Method B.---A solution of 9 g. (0.047 mole) of XIV in glacial acetic acid was reduced with Raney nickel in a Parr low pressure hydrogenation apparatus. The theoretical amount of hydrogen was rapidly absorbed. The solution was filtered into an excess of concentrated hydrochloric acid. The resulting red solution was concentrated in vacuo to a low volume. After slight dilution with ethanol, the addition of ether separated a red sirup which solidified after extensive stirring with a rod to yield 9.5 g. (82%) of brown solid; m.p. 205-206° (dec.) After purification as in Method A, light brown solid was obtained; m.p. 219-220° (dec.)(IIIa).

Anal. Calcd. for $C_{14}H_{19}N_3O.3HCl$: C, 47.40; H, 6.25. Found: C, 47.02; H, 6.14.

5-(7-Chloro-4-quinolylamino)-8-quinolinol Dihydrochloride Hemihydrate (XVII).---A solution of 13.5 g. (0.058 mole) of VII and 11.5 g. (0.058 mole) of 4,7-dichloroquinoline (XV) in 400 ml. of ethanol was heated at reflux for three hours. After standing overnight, a grey-green solid was separated by filtration and washed with hot ethanol to yield 19.0 g. (81%); m.p. 300° (dec.). For an analytical sample, a portion of the product was dissolved in methanol with heating. Ethanol was added and the methanol boiled off to produce a green solid after cooling.

Anal. Calcd. for $C_{18}H_{12}ClN_3O.2HCl.\frac{1}{2}H_2O$: C, 53.55; H, 3.75. Found: C, 53.43; H, 3.73.

5-(7-Chloro-4-quinolylamino)-7-(1-piperidylmethyl)-8-quinolinol Hydrate (XVIII).---The free base of XVII was prepared by dissolving the hydrochloride (XVII) in water and precipitating the yellow base with ammonium hydroxide; crude m.p. 142-143°.

A solution of 1.2 g. (0.0036 mole) of the free base of XVII, 0.11 g. (0.0037 mole) of paraformaldehyde, and 0.33 g. (0.0039 mole) of piperidine in 100 ml. of ethanol was refluxed for two hours. The volatile materials were then taken off in vacuo on the steam bath until a white solid

started to come out of solution. Cooling and trituration with water produced 1.4 g. (93%) of slightly red solid; m.p. 203-204°. Several recrystallizations from acetone yielded white crystals; m.p. 212°. This compound is soluble in 5% hydrochloric acid and insoluble in 5% sodium hydroxide solution.

Anal. Calcd. for $C_{24}H_{23}ClN_4O.\frac{1}{4}H_2O$: C, 68.07; H, 5.71. Found: C, 68.08, 68.12; H, 5.65, 5.68.

m-Chloroacetanilide (XX).---A solution of 391 g. (3.06 mole) of m-chloroaniline (XIX) in 370 g. of glacial acetic acid was refluxed for twenty hours. The reaction mixture was poured into an excess of ice water. A dark liquid separated which turned into white crystals on stirring; 445 g. (85%) m.p. 70-71° (reported m.p. 72.5°)[47].

Nitration of m-Chloroacetanilide.---A mixture of 262 g. (4.16 mole) of fuming nitric acid and 236 g. (3.93 mole) of glacial acetic acid was slowly dropped into a solution of 445 g. (2.61 mole) of XX in 424 g. (4.15 mole) of acetic anhydride and 236 g. (3.93 mole) of glacial acetic acid with the temperature between 0° and 5°. The mixture was allowed to come slowly to room temperature with stirring. The acid solution was then poured onto ice. The resulting brown solid was pressed under a rubber dam on a Buchner funnel and then dried in a large vacuum dessicator over successive fresh portions of phosphorous pentoxide. The dry

powder, a mixture of isomers, was extracted with 500 ml. of benzene in a continuous extraction to yield 254 g. (45%) of 2-nitro-5-chloroacetanilide (XXI); m.p. 114-117° (reported m.p. 117-118°)[24].

5-Chloro-8-nitroquinoline (XXII).---A homogeneous mixture of 15 g. (0.07 mole) of XXI, 10.6 g. of arsenic pentoxide, and 51 ml. of previously dehydrated glycerol was treated with 28.7 ml. of concentrated sulfuric acid. Heat was applied with a luminous flame until a vigorous reaction had started. When the reaction had subsided, the flask was allowed to stand for two hours. The reaction mixture was poured into ice water and filtered through porous plate. Ammonium hydroxide was added to the filtrate to separate 9.8 g. (68%) of brown solid; m.p. 123-124°. The product is purified by recrystallization from 50% acetic acid; m.p. 135-136° same as reported[24].

8-Nitro-5-quinolinol (XXIII).---A solution of 4 g. (0.19 mole) of XXII and 12.0 g. of potassium hydroxide in 80 ml. of ethanol and 120 ml. of water was refluxed ten hours. The addition of an excess of ether forced the yellow potassium salt from solution. The salt was dissolved in water and neutralized with acetic acid to produce 3.2 g. (86%) of yellow solid; m.p. 255-257° (dec.)(reported m.p. 257-258°)[24].

8-Nitro-6-piperidylmethyl-5-quinolinol Hydrochloride (XXVII).---A heated solution of 0.40 g. (0.013 mole) of paraformaldehyde and 1.5 ml. (0.015 mole) of piperidine in ethanol was added to 2.5 g. (0.013) mole of XXIII in 1.5 l. of absolute ethanol. The solution was concentrated to about 50 ml. which yielded upon cooling 2.5 g. (83%) of yellow solid; m.p. 124°. The base was converted to the hydrochloride which was recrystallized from ethanol to yield yellow crystals; m.p. (gathers at 140-141°) 193-194° (dec.).

Anal. Calcd. for $C_{15}H_{17}N_3O_3HCl$: Cl, 10.92. Found: Cl, 11.10.

8-Amino-5-quinolinol Dihydrochloride (XXIV).---XXIII (11.8 g.) was reduced in essentially the same manner as V: i.e., chemically with stannouschloride and concentrated hydrochloric acid to yield 10.5 g. (73%) of yellow crystals; m.p. 252-255° (dec.).

8-(7-Chloro-4-quinolylamino)-5-quinolinol Dihydrochloride Hemihydrate (XXV).---A solution of 2.5 g. (0.011 mole) of XXIV and 2.1 g. (0.011 mole) of XV in ethanol was refluxed for two hours before 3.7 g. (87%) of yellow flakes separated; m.p. 265-270° (dec.). The light product was purified by two recrystallizations from ethanol; 281-282° (dec.)

Anal. Calcd. for $C_{18}H_{12}ClN_3O.2HCl.\frac{1}{2}H_2O$: C, 53.55; H, 3.75. Found: C, 53.27; H, 4.30.

8-(7-Chloro-4-quinolylamino)-6-(1-piperidylmethyl)-5-quinolinol (XXVI).---A heated solution of 0.39 g. (0.015 mole) of paraformaldehyde and 4.5 ml. (0.045 mole) of piperidine in ethanol was added to a solution of 6 g. (0.015 mole) of XXV in 400 ml. of ethanol. The solution was heated at reflux for thirty minutes and the volatile materials removed in vacuo. The yellow residue was extracted with ethyl ether in a Soxhlet extractor. After drying over sodium sulfate, the ether was evaporated under a stream of dry air to leave 4.4 g. (69%) of yellow crystals; m.p. 182-183°. The product may be recrystallized from ethanol; m.p. 186°. It is soluble in 5% hydrochloric acid and insoluble in 5% sodium hydroxide solution.

Anal. Calcd. for $C_{24}H_{23}ClN_4O$: C, 68.81; H, 5.53. Found: C, 69.25; H, 5.73.

8-Nitro-6-quinolinol (XXIX).---A suspension of 50 g. (0.246 mole) of 6-methoxy-8-nitroquinoline (XXVIII) in 250 ml. of 48% hydrobromic acid was heated slowly to boiling over the duration of one hour. The dark solution was refluxed for four hours when yellow crystals came out of solution. The product was separated by filtration, suspended in water, and made alkaline with 20% sodium hydroxide solution. The dark solution was filtered through a glass funnel and neutralized with 5 N hydrochloric acid to separate 42.7 g. (91%) of crystals; m.p. 227-228° (dec.) (reported m.p. 226-228°)[29].

8-Amino-6-quinolinol Dihydrochloride (XXX).---XXIX (6.0 g.) was reduced using the procedure of VII and XXIV to yield 2.9 g. (40%) of yellow crystals; m.p. 242-243° (dec.).

8-(7-Chloro-4-quinolylamino)-6-quinolinol Dihydrochloride Monohydrate (XXXI).---A solution of 2.3 g. (0.01 mole) of XXIV and 2.0 g. (0.01 mole) of XV in 100 ml. of ethanol was heated at reflux for fifteen minutes when 2.9 g. (71%) of red-yellow crystals came out of solution; m.p. 283-285° (dec.). The product was recrystallized from ethanol; m.p. 295° (dec.).

Anal. Calcd. for $C_{18}H_{13}ClN_3O.2HCl.1H_2O$: C, 52.25; H, 3.90. Found: C, 52.33; H, 4.12.

5-Diethylaminomethyl-8-nitro-6-quinolinol (XXXIV).---A solution of 5 g. (0.026 mole) of XXIX, 0.8 g. (0.026 mole) of paraformaldehyde, and 3 ml. (0.026 mole) of diethylamine in 400 ml. of ethanol was refluxed for two hours. A small amount of dark solid was removed from the solution by filtration. The volume of the solution was reduced until cooling and stirring produced 1.g. of yellow solid; m.p. 125-127° (dec.). The remainder of the base was obtained by passing hydrogen chloride gas into the alcoholic solution which had been diluted with ethyl ether, dissolving the solid in water, and neutralizing with sodium hydroxide solution. The total yield was 4.5 g. (62%) of yellow crystals from aceton; m.p. 141-142° (dec.).

Anal. Calcd. for $C_{14}H_{17}N_3O_3$: C, 61.07; H, 6.23. Found: C, 61.12; H, 5.95.

8-Methoxy-4-quinolinol (XL).---A solution of 22 g. (0.12 mole) of oxalacetic ester (XXXVI) and 24.6 g. (0.20 mole) of o-anisidine in 100 ml. of glacial acetic acid was heated for four hours at 40-50°. The solution was allowed to stand for 20 hours and then poured into ice water. Neutralization with 20% sodium hydroxide solution caused the separation of a heavy oil which was extracted thrice with 200 ml. of ethyl ether. The combined ether portions were extracted in turn with two portions of 300 ml. of 0.7 N hydrochloric acid and with two portions of 160 ml. of 0.7 N sodium hydroxide solution. After drying over anhydrous potassium carbonate, the ether was evaporated to leave a dark sirup which solidified on cooling and stirring to yield 24.6 g. (72%) of orange solid (XXXVII); m.p. 59-60°.

The powdered acrylate (XXXVII) was slowly added to 200 ml. of mineral oil (Diphenyl ether can also be used with good results.) preheated to 250° with stirring over a ten minute period. The mixture was heated at that temperature for 5 minutes longer and then allowed to cool. An excess of Skellysolve B was added to separate a thick liquid. After decantation of the supernatent solvent, the sirup was crystallized by extensive stirring with a rod in Skellysolve B into 19.3 g. (93%) of tan solid; m.p. 101-103°.

A solution of 19 g. (0.077 mole) of 2-carbethoxy-8-methoxy-4-quinolinol (XXXVIII) in 200 ml. of 5% sodium hydroxide solution was refluxed for two hours, then cooled and filtered through a porous plate funnel. The dark solution was acidified with 10% hydrochloric acid to yield 16.5 g. (98%) of tan solid; m.p. 242° (dec.).

The acid (XXXIX) was slowly dropped into 100 ml. of mineral oil heated at 270° with stirring. The mixture was maintained at 270° for five minutes longer. Upon cooling, a glassy solid formed on the sides of the beaker. Skellysolve B was added and the mixture was filtered to yield 13.0 g. (99%) of impure product (XL); m.p. 131° (dec.) (reported m.p. 168-169°). This solid was recrystallized from water to yield 6.9 g. (53%) of the hydrate; m.p. 130-131° (reported m.p. 134-135°)[31].

4-Chloro-8-methoxyquinoline (XLI).---A mixture of 16.8 g. of phosphorous pentoxide and 16.8 g. of phosphorous oxychloride was heated at 70-80° (oil bath temperature) while 13.3 g. (0.076 mole) of XL was slowly added. The oil bath was heated at 130-140° for thirty minutes then the temperature was raised to 150-160° under vacuum applied with the water pump until the excess phosphorous oxychloride had been removed. The cooled residue was added to a mixture of ice and water. After filtering, the dark solution was neutralized with 10% sodium hydroxide solution to yield 9.7 g. (66%) of pink solid; m.p. 77° (reported m.p. 79-80°)[31].

4-Chloro-8-quinolinol (XLII).---A solution of 9.5 g. (0.049 mole) of XLI in a mixture of 61 ml. of concentrated sulfuric acid and 36 ml. of water was refluxed for five and one-half hours. The acid solution was poured over ice and neutralized with ammonium hydroxide to separate a green solid. This solid was stirred in 500 ml. of 2% sodium carbonate solution for two hours, then separated by filtration, washed, and dried to yield 8.2 g. (88%) of grey-green solid; m.p. 139-141° (dec.) A sample for analysis was prepared by vacuum sublimation and recrystallization from ethanol to yield beautiful, white crystals; m.p. 142-143°.

Anal. Calcd. for C_9H_6ClNO: C, 60.18; H, 3.37. Found: C, 59.98; H, 3.36.

4-(4-Chloroanilino)-8-quinolinol Hydrochloride. (XLIV).---A solution of 7.2 g. (0.04 mole) of XVLL and 5.2 g. (0.04 mole) of p-chloroaniline (XLIII) in 400 ml. of ethanol was refluxed for three hours. The solution was concentrated and diluted with ethyl ether to separate 8.8 g. (71%) of green solid; m.p. 289-292° (dec.). A sample was recrystallized from isopropanol with difficulty; m.p. 306-307° (dec. unevenly).

Anal. Calcd. for $C_{15}H_{11}ClN_2O.HCl$: C, ; H, . Found: C, ; H, .

4-(4-Chloroanilino)-7-(1-piperidylmethyl)-8-quinolinol (XLV).---A previously heated solution of 0.20 g. (0.0067 mole) of paraformaldehyde and 1.3 ml. (0.013 mole) of piperidine in ethanol was mixed with a solution of 2 g. (0.0066 mole) of XLIV. The mixture was boiled on the steam bath for 25 minutes and then evaporated to dryness in vacuo. The green residue was extracted with ethyl ether in a Soxhlet extractor. The ether was evaporated under a stream of dry air to leave 1.6 g. (62%) of yellow powder; m.p. 179-181° (dec.). A sample for analysis was recrystallized four times from ethanol; m.p. 206-207° (dec.).

Anal. Calcd. for $C_{21}H_{22}ClN_3O$: C, ; H, .
Found: C, ; H, .

Quinolinol Amebacides

5-Chloro-7-diethylaminomethyl-8-quinolinol Dihydrochloride (XLVII).---5-Chloro-8-quinolinol nitrate (XLVI)[a] was dissolved in water and an excess of sodium hydroxide solution was added to the cooled solution. After the alkaline solution had been filtered, XLVI was separated by the addition of acetic acid; m.p. 127-128° (reported m.p. 128-129°)[49].

A solution of 8 g. (0.045 mole) of XLVI, 1.35 g. (0.045 mole) of paraformaldehyde, and 5 ml. (0.048 mole) of

---

a XLVI was furnished by the Chemistry Department of the University of Cincinnati.

diethylamine in 500 ml. of ethanol was refluxed for one and one-half hours. Some dark solid was removed from the cooled solution by filtration and the volatile materials were removed at the water pump until there remained only a dark sirup which was dissolved in ether. A slow stream of hydrogen chloride gas separated 11.2 g. (74%) of yellow solid; m.p. 195-196° (dec.). Purification was accomplished by recrystallization from ethanol; m.p. 197-198° (dec.)

Anal. Calcd. for $C_{14}H_{17}ClN_2O.2HCl$: Cl, 21.00. Found: Cl, 21.08.

5-Bromo-8-quinolinol (XLVIII).---An acetic acid solution of 32 g. (0.20 mole) of bromine was slowly added to an agitated solution of 29 g. (0.20 mole) of IV in acetic acid over a two hour period. The precipitate was separated by filtration and extracted with hot water. The addition of sodium acetate solution caused the separation of 10.0 g. (23%) of XLVIII; m.p. 108-109°. The solid was recrystallized from ethanol; m.p. 124-125° (reported m.p. 124°).

5-Bromo-7-diethylaminomethyl-8-quinolinol Dihydrochloride (XLIX).---A solution of 4 g. (0.018 mole) of XLVIII, 0.54 g. (0.018 mole) of paraformaldehyde, and 1.9 ml. (0.018 mole) of diethylamine in 160 ml. of ethanol was refluxed for one hour. The solution was filtered and concentrated at the water pump to a low volume. Hydrogen chloride gas was then

passed through the solution which had been diluted with ether to form a sticky, yellow solid. The supernatent liquid was decanted from the solid which was immediately dissolved in hot ethanol. The alcoholic solution was filtered, concentrated, and cooled. Vigorous stirring with a rod was necessary to separate 3.5 g. (51%) of golden solid; m.p. 182-183° (dec.). A sample was purified for analysis by several recrystallizations from ethanol; m.p. 197-198° (dec.).

Anal. Calcd. for $C_{14}H_{17}BrN_2O.2HCl$: C, 44.00; H, 5.01. Found: C, 43.71; H, 5.02.

8-Chloro-6-quinolinol (LII)[36].---A solution of 5 g. (0.026 mole) of 8-chloro-6-methoxyquinoline (LI) in 50 ml. of 48% hydrobromic acid was refluxed for six hours. The solution was cooled and enough 20% sodium hydroxide solution was added to dissolve the solid which initially separated. The dark solution was filtered and neutralized with 10% hydrochloric acid. A light pink solid was separated by filtration, washed with water, and dried on a porous plate; 4.5 g. (96%) m.p. 236-237° (dec.). The solid was purified by recrystallization from ethanol; m.p. 237-238° (dec.).

Anal. Calcd. for C_9H_6ClNO: C, 60.18; H, 3.37. Found: C, 60.08; H, 3.49.

8-Chloro-5-(1-piperidylmethyl)-6-quinolinol Dihydrochloride Sesquihydrate (LIII).---A solution of 3 g. (0.017 mole) of LII in alcohol was added to a previously heated solution of 0.51 g. (0.017 mole) of paraformaldehyde and 1.7 ml. (0.017 mole) of piperidine in ethanol. The clear solution was refluxed for five hours and concentrated to about 30 ml. Hydrogen chloride gas was bubbled slowly through the solution to separate a brown solid. Ether was added to complete the separation of 5.4 g. (88%) of LIII; melts indefinately above 220°. The light tan solid was recrystallized from ethanol for analysis.

Anal. Calcd. for $C_{15}H_{17}ClN_2O.2HCl.1\frac{1}{2}H_2O$: Cl, 18.82. Found: Cl, 18.82.

The free base was obtained by dissolving LIII in water, neutralizing the solution, and extracting with ether. The dried ether solution was evaporated to dryness under a stream of air to leave the crude base; m.p. 97-98° (dec.). The free base is insoluble in 5% sodium hydroxide solution.

8-Bromo-6-methoxyquinoline (LIV).--- Nineteen grams (0.28 mole) of sodium nitrite was added to 120 ml. of concentrated sulfuric acid with stirring and cooling at a rate which kept the temperature below 10°. When the sodium nitrite had been added, the mixture was heated to 70° at which temperature a violent reaction took place and a clear solution resulted. The cooling bath was replaced and a solution of

40 g. (0.23 mole) of 8-amino-6-methoxyquinoline (L) in glacial acetic acid slowly added to maintain a temperature of 18-20°.

During this time, a solution of cuprous bromide in 75 ml. of 48% hydrobromic acid was prepared. The diazotization mixture was slowly added to the bromide mixture with shaking and cooling under the water tap. The mixture was then heated on the steam bath for one hour and allowed to stand at room temperature overnight.

The mixture was neutralized under cooling with ammonium hydroxide. A black tar was separated from the solution by filtration and extracted with dilute hydrochloric acid. The acid solution was neutralized with sodium hydroxide solution to separate a dark solid which was extracted with one liter of ether. The aqueous solution was filtered and the resulting dark solid also extracted with ether in a Soxhlet extractor. Hydrogen chloride gas was passed into both dried ether solutions to separate 30.9 g. (49%) of orange solid; m.p. 213-214° (dec.). Further purification can be accomplished by recrystallization from ethanol. The hydrochloride (LIV) was in part converted to the free base which is known[38].

8-Bromo-6-quinolinol (LV).---A solution of 5 g. (0.018 mole) of LIV in 60 ml. of 48% hydrobromic acid was refluxed for five hours. A slight excess of sodium hydroxide

solution was added to thesolution. After filtering, the addition of hydrochloric acid separated 3.9 g. (95%) of brown solid; m.p. 242-243° (dec.). A sample was purified for analysis by vacuum sublimation at 0.2-0.3 mm. followed by several recrystallizations from ethanol; m.p. 245° (dec.).

Anal. Calcd. for C_9H_6BrNO: C, 48.24; H, 2.70. Found: C, ; H, .

8-Bromo-5-(1-piperidylmethyl)-6-quinolinol (LVI).---A solution of 4 g. (0.018 mole) of LV in ethanol was added to a previously heated solution of 0.56 g. (0.19 mole) of paraformaldehyde and 1.8 ml. (0.018 mole) of piperidine in ethanol. The mixture was refluxed for twenty minutes, then concentrated to about 50 ml. at the water pump. Cooling and stirring with a rod separated 4.0 g. (70%) of tan solid; m.p. 137° (dec.). A sample for analysis was prepared by several recrystallizations from ethanol to yield tan plates; m.p. 139° (dec.).

Anal. Calcd. for $C_{15}H_{17}BrN_2O$: C, 56.08; H, 5.34. Found: C, 55.86; H, 5.47.

8-Iodo-6-methoxyquinoline (LVII).---A solution of 7.2 g. (0.104 mole) of sodium nitrite in 15 ml. of water was slowly added to a cooled and agitated solution of 17.4 g. (0.10 mole) of L in 14.2 g. of concentrated sulfuric acid diluted by 50 g. of crushed ice and 50 ml. of water so that

the temperature was maintained at 0-5°. The mixture was stirred for fifteen minutes longer.

The diazotization mixture was quickly poured into a cold solution of 20 g. of potassium iodide in water followed immediately by an excess of copper bronze powder. The mixture was heated on the steam bath for two hours at 75-80° with efficient stirring. The red residue was filtered from the cooled solution and, after drying, exhaustively extracted with benzene. After the benzene had been evaporated under a stream of dry air, the black residue was dissolved in hot ethanol at once. The alcoholic solution was concentrated and cooled to separate 7.2 g. (25%) of pure, red crystals; m.p. 109° (dec.)(reported m.p. 105-107°)[36].

8-Iodo-6-quinolinol (LVIII).---Five grams (0.018 mole) of LVII was dissolved in 50 ml. of 48% hydrobromic acid. The salt precipitated but redissolved during the progress of the four hour reflux period. The clear, red solution was allowed to stand overnight. A slight excess of sodium hydroxide solution was added to the acid solution with cooling. Acidification with dilute hydrochloric acid separated 4.1 g. (89%); 246-248° (dec.). A sample was purified by vacuum sublimation at 0.2-0.3 mm. and recrystallized from ethanol to yield pink crystals; m.p. 259-260° (dec.).

Anal. Calcd. for C_9H_6INO: C, 39.88; H, 2.23. Found: C, ; H,

8-Iodo-5-(1-piperidylmethyl)-6-quinolinol (LIX).---A solution of 2.5 g. (0.0092 mole) of LVIII in ethanol was added to a previously heated solution of piperidine and 0.28 g. (0.0093 mole) of paraformaldehyde in ethanol. The clear solution was heated on the steam bath for twenty minutes and then concentrated to 40 ml. Cooling and stirring with a rod separated 2.8 g. (86%) of brown solid; m.p. 171-172° (dec.) A sample was purified for analysis by recrystallization from ethanol to yield beautiful, tan crystals; m.p. 178° (dec.).

Anal. Calcd. for $C_{15}H_{17}IN_2O$: C, 48.92; H, 4.66. Found: C, 49.23; H, 4.85.

O,N-Diacetyl-2-aminophenol (LXI).---A solution of 21.8 g. (0.20 mole) of o-aminophenol (LX) in pyridine with 42 ml. of 99-100% acetic anhydride was refluxed for one and one-half hours. The solution was concentrated and let stand overnight to separate 30.5 g. (93%) of crystals; m.p. 123-124° (reported m.p. 124.5°)[41].

O,N-Diacetyl-2-amino-5-chlorophenol (LXII).---A stream of chlorine gas was passed through a cooled solution of 30 g. (0.18 mole) of LXI in 250 ml. of chloroform until the theoretical increase in weight had been realized. The solution was concentrated and cooled to separate 19.6 g. (54%) of tan solid; m.p. 166-167° (reported m.p. 163-164°)[39].

6-Chloro-8-quinolinol (LXIII).---A mixture of 19.5 g. (0.10 mole) of LXII, 25 g. of glycerine, 15.5 g. of arsenic pentoxide, and 15 ml. of concentrated sulfuric acid was heated at 155° for four hours. The dark sirup was poured into ice water and neutralized with ammonium hydroxide. The black solid was separated by filtration, washed with water, and either extracted with ammonium hydroxide or sublimed directly. Neutralization of the filtered basic solution produced 6.8 g. (38%) of white crystals; m.p. 141° (reported m.p. 140°)[42].

6-Chloro-7-(1-piperidylmethyl)-8-quinolinol Dihydrochloride Hydrate (LXIV).---A solution of 0.37 g. (0.012 mole) of paraformaldehyde and 1.2 ml. (0.012 mole) of piperidine in ethanol was mixed with an alcoholic solution of 2.2 g. (0.012 mole) of LXIII. The mixture was heated for 10 minutes on the steam bath and then concentrated at the pump to a small volume. Hydrogen chloride gas was passed into the solution which was then diluted with ether to separate a heavy, black sirup. Trituration with several fresh portions of acetone produced 3.0 g. (72%) of grey solid; m.p. 190-192° (dec.). A sample was recrystallized several times from isopropanol to yield an off-white solid; m.p. 198-199° (dec.).

Anal. Calcd. for $C_{15}H_{17}ClN_2O.2HCl.H_2O$: C, 49.60; H, 5.65. Found: C, 49.67; H, 5.89.

4-Iodo-2-nitroanisole (LXVI).---A mixture of 70 g. (0.45 mole) of o-nitroanisole (LXV), 140 ml. of concentrated nitric acid, and 90 g. of iodine was stirred overnight. The thick mixture was diluted with water and sulfur dioxide gas passed through until most of the excess iodine had disappeared. The yellow solid was separated by filtration, washed with water, and dried on a porous plate to yield 124 g. (98%) of crystals; m.p. 94-95° (reported m.p. 98°)[44]. If any iodine remains after the sulfur dioxide treatment, recrystallization from alcohol is advisable.

2-Amino-4-iodoanisole (LXVI).---A mixture of 220 g. (0.79 mole) of LXVI and 720 ml. of concentrated hydrochloric acid was stirred efficiently while 220 g. of mossy tin was slowly added. When the tin had been added, the mixture was stirred for one and one-half hours and neutralized with sodium hydroxide solution with cooling. The cooled reaction mixture was then extracted with 3 l. of ethyl ether. The dried ether solution was concentrated in vacuo to leave 193 g. (98%) of white crystals; m.p. 73-74° (reported m.p. 87°)[44]. The product may be purified further by recrystallization from ethanol but such procedure usually causes darkening of the material.

Ethyl β-Carbethoxy-β (3-iodo-6-methoxyanilino)-acrylate (LXVIII) Method A.---A solution of 102.6 g. (0.41 mole) of LXVI and 74 g. (0.39 mole) of XXXVI in 300 ml. of glacial acetic acid was heated for five hours at 45-50° and

then let stand overnight. The acid solution was poured into ice water and neutralized with sodium hydroxide solution with cooling. The oil which separated was dissolved in ether. The combined ether extracts were washed with dilute hydrochloric acid and then with dilute sodium hydroxide solution. The dried ether solution was concentrated on the steam bath until only a thick sirup remained which solidified into 130.6 g. (83%) of yellow crystals upon cooling and stirring with a rod; m.p. 71-72°. A sample was purified for analysis by recrystallization from ethanol; m.p. 79°.

Anal. Calcd. for $C_{15}H_{18}INO_5$: C, 42.97; H, 4.33. Found: C, ; H, .

Method B[46].---A suspension of 25 g. (0.087 mole, m.p. 241-242° (dec.)) of the hydrochloride of LXVIII, 25 g. of anhydrous sodium sulfate, and 19.2 g. (0.091 mole) of the sodium salt of XXXVI in 200 ml. of absolute ethanol was stirred at room temperature for twenty hours. The mixture was poured into about 1 l. of water and the oil which separated was extracted with ether. The ether extract was dried and concentrated to yield 31.3 g. (86%) of yellow crystals; m.p. 72-73°.

2-Carbethoxy-5-iodo-8-methoxy-4-quinolinol (LXIX).---One hundred and thirty grams (0.31 mole) of LXVIII was added to 300 ml. of preheated diphenyl ether at 240°. The solution was then refluxed for thirty-five minutes, cooled, and diluted

with Skellysolve B to separate an oil which was exhaustively triturated with successive fresh portions of Skellysolve to produce 76.4 g. (80%) of light brown solid; m.p. 118-119° (dec.). A sample for analysis was purified by several recrystallizations from isopropanol; m.p. 157° (dec.).

Anal. Calcd. for $C_{13}H_{12}INO_4$: C, 41.84; H, 3.24. Found: C, 41.58; H, 3.34.

2-Carboxy-5-iodo-8-methoxy-4-quinolinol (LXX).---A suspension of 76.4 g. (0.20 mole) of LXIX in 500 ml. of 10 per cent sodium hydroxide solution was refluxed for two hours. The cooled solution was filtered and neutralized with concentrated hydrochloric acid to yield 71 g. (100%) of yellow solid; m.p. 252-253° (dec. with evolution of gas). A sample was purified by recrystallization from ethanol to yield yellow crystals; m.p. 260° (dec.).

Anal. Calcd. for $C_{11}H_8INO_4$: C, ; H, . Found: C, ; H, .

5-Iodo-8-methoxy-4-quinolinol (LXXI).---Ten grams (0.029 mole) of LXX was dropped slowly into 80 ml. of diphenyl ether with stirring and heating at 225-230°. The mixture was heated at that temperature for ten minutes and then cooled to separate, after washing with ethyl ether, a brown solid. The impure mixture was stirred in 400 ml. of 2% sodium carbonate solution for two hours, then filtered and

washed with water to recover 6.9 g. (79%) of brown powder; m.p. 245° (dec.). A sample was recrystallized several times from ethanol for analysis; m.p. 248°.

Anal. Calcd. for $C_{10}H_8INO_2 \cdot \frac{1}{2}H_2O$: C, 38.73; H, 2.92. Found: C, 39.00; H, 2.75.

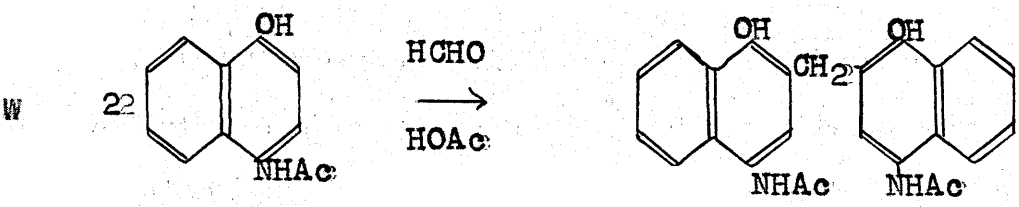
4-Chloro-5-iodo-8-methoxyquinoline (LXXII).---A solution of 13.5 g. (0.065 mole) of phosphorous pentachloride in an excess of phosphorous oxychloride was heated to 105-110° with stirring, at which temperature 19.4 g. (0.065 mole) of LXXI was slowly added. The oil bath was then raised to 135-140° for thirty minutes. The excess phosphorous oxychloride was removed at the water pump. The sticky residue was added slowly to an agitated mixture of benzene and dilute sodium hydroxide solution. When the reaction residue had been added, the solution was made basic with sodium carbonate. The basic solution was extracted a second time with benzene. The benzene extracts were combined and evaporated under a stream of air to leave 10.3 g. (50%) of impure brown solid; m.p. 97-99°. The product was vacuum sublimed at as low a temperature as possible followed by several recrystallizations from ethanol to yield a white solid; m.p. 114-115°.

Anal. Calcd. for $C_{10}H_7ClINO$: C, 37.24; H, 2.21. Found: C, ; H, .

4-(3-diethylaminomethyl-4-hydroxyanilino)-5-iodo-8-methoxyquinoline (LXXIV).---A solution of 2 g. (0.0063 mole) of LXII and 1.7 g. (0.0064 mole) of 4-amino-2-diethylaminomethylphenol dihydrochloride (LXXIII) in 200 ml. of ethanol was refluxed for two hours and then concentrated to 30 ml. The alcoholic solution was poured into an excess of ether to separate a brown sirup which was crystallized by extensive stirring with a rod in acetone to 3.2 g. (93%) of yellow crystals; m.p. 116° (dec.). The product is very hygroscopic when recrystallization is attempted; however, a small portion was precipitated from isopropanol solution with acetone to yield yellow crystals; m.p. 182-183° (dec.).

Anal. Calcd. for $C_{21}H_{24}IN_3O_2.2HCl$: C, ; H, . Found: C, ; H, .

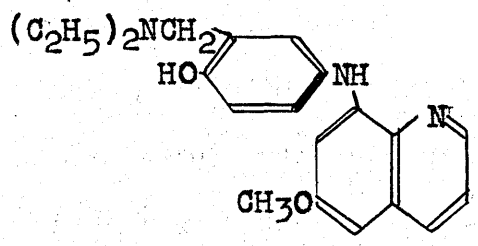
VI. APPENDIX



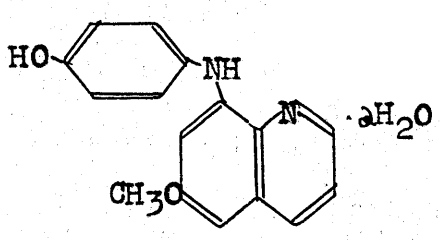
LXXV LXXVI

When IX (page 96) was thought to have interesting antimalarial activity, the naphthalene congener (LXXVI) of IX was made. Since LXXVI was found to be exceptionally insoluble and since IX was subsequently found to be inactive, no further work along this line was attempted.

2,2'-Methylene-bis-(4-acetamido-1-naphthol)(LXXVI).--- A solution of 12 g. (0.60 mole) of 4-acetamido-1-naphthol (LXXV, prepared by acetylation of 4-amino-1-naphthol hydrochloride in water with sodium acetate and acetic anhydride) and 0.9 g. (0.30 mole) of paraformaldehyde in acetic acid was refluxed overnight. Two grams (16%) of white, cottony solid was recovered; m.p. 294-296° (dec.). The product was insoluble in all available solvents including dilute alkali.



LXXIX



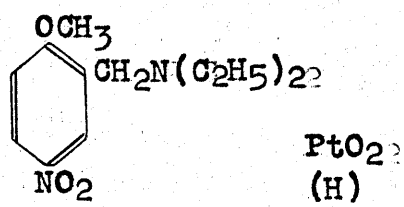
LXXX

Several attempts were made to prepare the 8-amino-6-methoxyquinoline analogue of Camoquin (LXXIX). During the progress of this work, 8-(4-hydroxyanilino)-6-methoxyquinoline (LXXIX) which had been prepared by Dr. J. H. Burckhalter[50] was remade and a satisfactory analysis obtained.

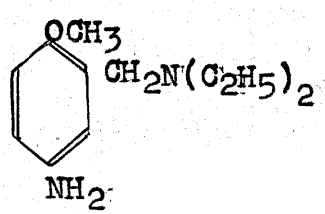
Anal. Calcd. for $C_{16}H_{14}N_2O.2H_2O$: C, 63.56; H, 6.00. Found: C, 63.37; H, 5.82.

The fact that the Mannich reaction could not be applied to LXXX had been indicated by Dr. Burckhalter's previous work and this was confirmed. Many attempts were made to condense the 8-halo-6-methoxyquinolines (LI, LIV, LVII) with various side chains which could lead to LXXIX; however, no positive results were obtained presumably because of the lability of the side chains to heat. During the progress of this work, 4-amino-2-diethylaminomethylanisole (LXXVIII) which had not been isolated before was prepared. It is interesting that LXXVIII can be distilled without decomposition.

X



PtO_2
(H)

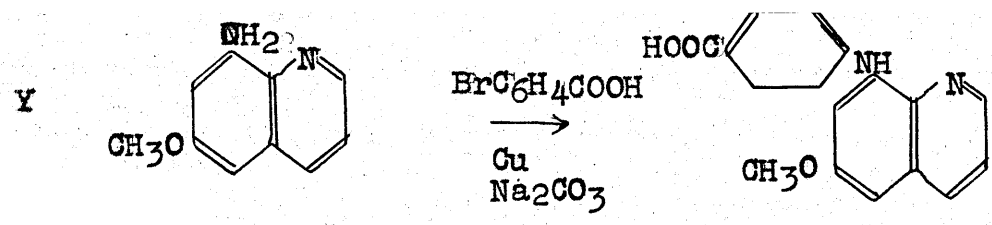


LXXVII

LXXVIII

4-Amino-2-diethylaminomethylanisole (LXXVIII).--- A water solution of 15 g. (0.055 mole) of 2-diethylaminomethyl-4-nitroanisole hydrochloride[2] (LXXVII) was neutralized with ammonium hydroxide and extracted with ether. The ether solution was immediately reduced catalytically with platinum oxide, filtered, and concentrated. The residue was distilled in vacuo to yield 8.5 g. (75%) of colorless liquid; b.p. 127-128° at 0.2 mm. n^{20} 1.5410. This sample decomposed slightly even in a sealed tube and hence was not analyzed.

Work along this line of synthesis will be continued by others in the near future.



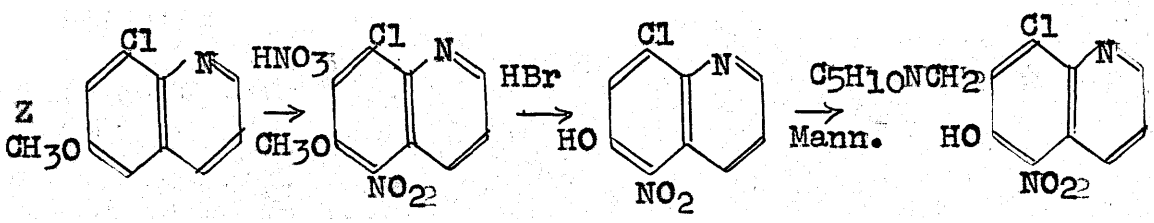
L LXXXII

4-(6-methoxy-8-quinolylamino)-benzoic acid (LXXXI), was prepared as the first step in the synthesis of a compound closely related to LXXIX. Subsequent steps were to be reduction of the carboxy group, replacement of the resulting alcohol group with a chloro atom, and condensation with

diethylamine. LXXI was prepared but was found very difficult to purify. It was found to be a hydrate. The lithium aluminum hydride reduction of LXXXI was unsuccessful because of its insolubility in the various ethers. Further work along this line was discontinued because of the limitations of time but will be resumed by others at a later date.

4-(6-Methoxy-8-quinolylamino)-benzoic acid (LXXXI).--- A mixture of 8.7 g. (0.05 mole) of L, 10.1 g. (0.05 mole) of p-bromobenzoic acid, 13.8 g. (0.10 mole) of potassium carbonate, and 0.2 g. of copper bronze powder in 200 ml. of water was refluxed with stirring for seventeen hours. The hot solution was filtered through a sintered glass filter and, after cooling, carefully acidified with dilute hydrochloric acid to separate 12.1 g. (82%) of impure, yellow solid; m.p. 168-171° (dec.). The solid was dissolved as well as possible in dilute hydrochloric acid, filtered, and neutralized with 10% sodium hydroxide solution. Recrystallization from acetone twice yielded a yellow solid; m.p. 219-220° (dec.).

Anal. Calcd. for $C_{14}H_{14}N_2O_3.2\frac{1}{4}H_2O$: C, 60.97; H, 5.56. Found: C, 60.93; H, 5.05.



LI LXXXII LXXXIII LXXIV

An attempt was made to prepare a hybrid (LXXXIV) of two compounds (XIV and XLVII) which have shown amebacidal activity. LXXXIV should, in addition, have a very active halogen. Purification of the intermediates was difficult because of the difficulty in recrystallization. The samples were purified by sublimation but good analytical results could not be obtained. The Mannich base (LXXXIV) apparently was formed but could not be separated from unreacted starting material by repeated recrystallization.

8-Chloro-6-methoxy-5-nitroquinoline (LXXXII).---A mixture of 45 g. of concentrated sulfuric acid and 45 g. of fuming nitric acid was cooled to 0° and 15 g. (0.078 mole) of LI slowly added. The mixture was heated at 75-85° for one hour when it was poured into a slurry of ice and water to separate 10.0 g. (54%) of yellow solid; m.p. 148-149°. A sample was sublimed in vacuo twice; m.p. 167-168°.

Anal. Calcd. for $C_{10}H_7ClN_2O_3$: C, 50.33; H, 2.96. Found: C, 51.22; H, 2.95.

8-Chloro-5-nitro-6-quinolinol (LXXXIII).---A solution of 4 g. (0.017 mole) of LXXXII in 100 ml. of 48% hydrobromic acid was refluxed for six hours. After the cooled solution had been made basic with sodium hydroxide solution, a large part of the sodium salt was insoluble. The orange solid was separated by filtration, dissolved in water, and neutralized with dilute hydrochloric acid to separate 2.7 g. (71%) of yellow crystals; 139-140° (dec.). A sample for analysis was purified by sublimation in vacuo with no increase in melting point.

Anal. Calcd. for $C_9H_5ClN_2O_3.\frac{1}{2}H_2O$: C, 47.18; H, 2.42. Found: C, 47.38; H, 2.48.

VII SUMMARY

A report* of exceptional antimalarial activity in an impure sample of 5-amino-7-diethylaminomethyl-8-quinolinol trihydrochloride was investigated. The conclusion was that the activity is inherent in the compound itself rather than in an impurity. The activity proved to be less than originally reported or about one-half that of quinine in avian malaria.

Several potential antimalarial drugs of the quinolinol series were synthesized including a position isomer of Camoquin, 4-(4-chloroanilino)-7-(1-piperidylmethyl)-8-quinolinol, and two isomers closely related to Camoquin, 5-(7-chloro-4-quinolylamino)-7-(1-piperidylmethyl)-8-quinolinol and 8-(7-chloro-4-quinolylamino)-6-(1-piperidylmethyl)-5-quinolinol. A third isomer of the latter two compounds could not be prepared. Detailed pharmacological data on these compounds are not available as yet.

A group of six potential amebacides was prepared. All were Mannich bases of the haloquinolinol series. In addition, considerable work was done in preparing the hybrid of Diodoquin and Camoquin, with the hope of obtaining a universal amebacide. Preliminary reports indicate that the Mannich base type of amebacide is active; however, the data is incomplete.

* All pharmacological work was done at Parke, Davis & Co., Detroit, Mich.

VIII. BIBLIOGRAPHY

1. Burckhalter and DeWald, private communication.
2. Burckhalter *et al.*, *J. Am. Chem. Soc.*, 70, 1363 (1948).
3. Schönnhöfer, *Z. physiol. Chem.*, 274, 1 (1942).
4. (a) Conan, *Am. J. Med.*, 6, 309 (1949).
   (b) Emmett, *J.A.M.A.*, 141, 22 (1949).
   (c) Murgatroyd and Kent, *Trans. Roy. Trop. Med. & Hyg.*, 42, 15 (1948).
5. Goodman and Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, N.Y., 1941, pp. 903-907.
6. Krantz and Carr, "The Pharmacologic Principles of Medical Practice," The Williams and Wilkins Co., Baltimore, Md., 1949, pp. 86-110.
7. Wiselogle, "A Survey of Antimalarial Drugs, 1941-1945," Edwards Bros., Ann Arbor, Mich., 1946.
8. *Science*, 103, 8 (1946).
9. L. T. Coggeshall, University of Chicago, private communication.
10. (a) Knoppers, *Nature*, 160, 606 (1949).
    (b) Williamson *et al.*, *Nature*, 159, 885 (1947).
    (c) Bishop and Birkett, *Nature*, 159, 884 (1947).
    (d) Williamson and Lourie, *Ann. Trop. Med. Parasit.*, 41, 278 (1947).
11. Ref. 5, pp. 930-942.
12. Ref. 6, pp. 156-162.
13. Nix, *New Orleans Med. Surg. J.*, 100, 108-118 (1947).
14. Manson-Bahr and Muggleton, *J. Trop. Med.*, 51, 23 (1948).
15. Arosemena, *New Orleans Med. Surg. J.*, 97, 892 (1945).

16. Gross, Indian Med. Gaz., 82, 452 (1947).

17. Lavier et al., Trop. Dis. Bull., 46, 469 (1949).

18. Wright and Coombes, Lancet, 1, 243 (1948).

19. Dennis et al., Am. J. Trop. Med., 29, 683 (1949).

20. (a) Jacobs and Heidelberger, J. Am. Chem. Soc., 39, 2218

(b) Lippmann and Fleissner, Monatsh., 10, 296 (1889).

21. (a) Albert and Magrath, Biochem. J., 41, 534 (1947).

(b) Kostanecki, Ber., 24, 150 (1891).

22. Ghosh et al., J. Ind. Chem. Soc., 22, 221 (1945).

23. W. F. Holcomb, unpublished work.

24. Fuson et al., J. Org. Chem., 12, 804 (1947).

25. Fourneau et al., Bull. soc. chim., 47, 738 (1930).

26. Lutz et al., J. Am. Chem. Soc., 68, 1324 (1946).

27. (a) Manske, Can. J. Res., 19B, 318 (1941).

(b) Elderfield, J. Am. Chem. Soc., 68, 1585 (1946).

28. Gattermann, Ber, 27, 1940 (1894).

29. Morgan and Tipton, J. Am. Chem. Soc., 68, 1570 (1946).

30. Matheus, Ber., 21, 1645 (1888).

31. Lauer et al., J. Am. Chem. Soc., 68, 1268 (1946).

32. Reitsema, Chem. Revs., 43, 43 (1948).

33. Ramsey, J. Am. Chem. Soc., 69, 1659 (1947).

34. Burckhalter et al., J. Am. Chem. Soc., 68, 1900 (1946).

35. Matsumora, J. Am. Chem. Soc., 49, 815 (1927).

36. Price, J. Am. Chem. Soc., 68, 2589 (1946).

37. Feldman and Wagner, J. Org. Chem., 7, 31 (1932).

38. Berkenheim and Antik, J. Gen. Chem. (U.S.S.R.), 11, 537 (1941); C.A., 35, 6962 (1941).

39. Theilacker, Ber. dtsch. chem. Ges., 71, 2066 (1938).

40. Bamberger, Ber., 36, 2050 (1903).

41. LeRosen and Smith, J. Am. Chem. Soc., 70, 2708 (1948).

42. Hoffmann, Bull. soc. chim. France, 1947, 969.

43. (a) Burckhalter et al., J. Am. Chem. Soc., 68, 1894 (1946).

(b) Decombe, Compt. rend., 196, 866 (1933).

44. Robinson, J. Chem. Soc., 109, 1084 (1916).

45. (a) Riegel et al., J. Am. Chem. Soc., 68, 2685 (1946).

(b) Wislicenus, Ann., 246, 317 (1888).

46. Lisk and Stacy, J. Am. Chem. Soc., 68, 2686 (1946).

47. Hodgman, "Handbook of Chemistry and Physics," Chemical Rubber Publishing Co., Cleveland, Ohio, 1942, p. 548.

48. Shionogi, Jap. pat. 162,066; C.A., 43, 2646 (1949).

49. Claus, J. prackt. Chem., 44, 444 (1891).

50. J. H. Burckhalter, unpublished work.

51. Pailer and Porschinski, Monatsh., 80, 94 (1949).

52. Blicke in Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N.Y., 1942, p. 303.

53. Alexander and Underhill, J. Am. Chem. Soc., 71, 4014 (1949).