

Approval Sheet

John A. Garman, Ph. D., 1946

Title of thesis: Synthetic Antimalarials

Thesis and abstract approved:

Nathan L. Drake

Nathan L. Drake
Professor of Organic Chemistry

September 15, 1947.

SYNTHETIC ANTIMALARIALS

By

John A. Gurnea

**Thesis submitted to the Faculty of the Graduate School
of the University of Maryland in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy**

1948

UMI Number: DP70355

All rights reserved

INFORMATION TO ALL USERS

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



UMI DP70355

Published by ProQuest LLC (2015). Copyright in the Dissertation held by the Author.

Microform Edition © ProQuest LLC.

All rights reserved. This work is protected against unauthorized copying under Title 17, United States Code



ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 - 1346

The author wishes to express his sincere appreciation to Professor Nathan L. Drake for his continued encouragement and assistance in the course of these researches.

TABLE OF CONTENTS

| | |
|---|----|
| I. INTRODUCTION | 1 |
| Sulfonamides | 2 |
| Aminoalcohols | 5 |
| 4-Aminoquinolines | 6 |
| Monoalkylguanidines | 12 |
| Dialkylguanidines | 20 |
| Biguanides | 23 |
| II. EXPERIMENTAL | 26 |
| 3'-Chloro-4'-dimethylamino-sulfanilamide (SN-5659; UM 17) | 28 |
| N ¹ -(5-bromo-1-naphthyl)-sulfanilamide (SN-7137; UM 30) | 31 |
| N ¹ -(5-quinelyl)-sulfanilamide (SN-8413; UM 39) | 33 |
| -(4'-Bromo-4-biphenyl)- -diisobutylaminoethanol Hydrochloride (SN-5321-4; UM 19) | 37 |
| -(4'-Bromo-4-biphenyl) -diethylaminoethanol Hydrobromide (SN-6622-13; UM 28) | 39 |
| 4-(1'-Diethylamino-4'-oxylamino)-6-methoxy-3-phenyl- quinoline Triphosphate (SN-1905-5; UM 47) | 39 |
| 4-(1'-Diethylamino-4'-oxylamino)-6-phenoxyquinoline (SN-10,899; UM 50) | 39 |
| 7-Chloro-4-(1'-diethylamino-6'-hexylamino)-quinoline Diphosphate (SN-9776-5; UM 34) | 41 |
| 4-(1'-Diethylamino-4'-amylamino)-7-phenoxyquinoline (SN-10,663; UM 55) | 41 |
| 7-Chloro-4-(3'-diethylaminocyclohexylamino)- quinoline Diphosphate Monohydrate (SN-12,107-3; UM 57) | 45 |

| | |
|---|----|
| 7-chloro-4-(4'-diethylaminocyclohexylamino)-quinoline Diphosphate (suspected <u>isotia</u>) (SM-13,166-5; UM 88 a) | 45 |
| 7-chloro-4-(4'-diethylaminocyclohexylamino)-quinoline (suspected <u>trans</u>) (SM-14,477; UM 88 a) | 45 |
| 7-chloro-4-(4'-diethylaminocyclohexylamino)-quinoline (suspected <u>cis</u>) | 46 |
| N ¹ -(2-(6-methoxy-8-quinolyloamino)-ethyl)-guanidine Dinitrate (UM 165 a) | 57 |
| N ¹ -(2-(6-methoxy-8-quinolyloamino)-propyl)-guanidine Dinitrate (UM 161 a) | 59 |
| N ¹ -(4-(6-methoxy-8-quinolyloamino)-butyl)-guanidine Dinitrate (UM 148 a) | 60 |
| N ¹ -(5-(6-methoxy-8-quinolyloamino)-amyl)-guanidine Dinitrate (UM 148 a) | 60 |

INTRODUCTION

The history of malaria therapy prior to 1941 has been extensively covered in the literature due to the vastness of the endemic areas and the enormous economic importance of the disease. The events leading to the partial displacements of the cinchona alkaloids, especially quinine, as the indicated therapy have also been fully covered,¹ as has the recent co-operative and concerted effort to discover compounds of greater value in the treatment of the disease.²

Ever since the cause and nature of malaria have been known and the various phases of the parasitic infection in the human host have been recognized attempts have been made to discover curative and prophylactic drugs. Therapy with the cinchona alkaloids and drugs having a similar action results only in the suppression of the symptomatic manifestations of the disease and not in any curative action. The ultimate aim of all malaria researches is to find a truly prophylactic drug, that is, one which can be administered before exposure to infection and which will prevent the further development of or will destroy the sporozoites, the form of the organism with which man is inoculated by the mosquito. The recent anti-malarial program produced approximately 100 compounds which were shown to have some degree of prophylactic activity.²

¹Goldman, Synthetic Antimalarials (Thesis, University of Maryland, College Park, Maryland, 1944).

²Wisselogle, Survey of Antimalarial Drugs 1941-1945 (Ann Arbor, Michigan: J. W. Edwards, 1946).

but none had the requisite activity to promote its adoption as a means of prophylaxis. The search for such a drug is continuing among compounds related to those shown to have some activity as well as among other compounds bearing no formal relationship.

The synthesis of potential antimalarial drugs during the last six years has sharply reflected the changing emphasis on different types of chemical compounds as the results of the screening tests, pharmacological investigations, and clinical studies were collected and evaluated. This changing emphasis is further reflected by the variation in the types of compounds reported in this thesis.

During the several years immediately preceding the outbreak of the recent war the investigation and use of various types of sulfa drugs had achieved a tremendous popularity, and some work had been done in an attempt to apply this type of compound in the chemotherapy of malaria. A review of the earlier chaotic reports of the value of sulfanilamide itself by Sinton³ revealed that while the drug was not efficacious in human or avian malaria it did have a considerable effect on P. knowlesi in monkeys. More recent work showed that sulfathiazole, sulfadiazine, and sulfanilamide

³Sinton, Hutton, and Shute, Ann. Trop. Med., 33, 37 (1959).

were effective against *P. lophurae* in ducks,⁴ and Coggeshall⁵ reported sulfadiazine to be to some extent effective against all types of human malaria. These facts, and the recognition by those who were coordinating the antimalarial research that sulfadiazine was a causal prophylactic in avian malaria, led to the synthesis of a large number of different types of sulfa drugs in the hope that a lead to a new and effective antimalarial agent might be uncovered. It was to this end that the compounds herein reported were prepared.

In general, the synthesis of these compounds consisted of coupling an appropriate amine or amine salt with *N*-acetylsulfanilyl chloride in pyridine with subsequent hydrolysis of the resultant acetyl derivative in either acidic or basic media depending upon the nature of the compound. A departure was made from this procedure in the case of the 3'-chloro-4'-dimethylaminosulfanilanilide where an ether solution of 5-chloro-4-dimethylaminocyaniline was coupled with *N*-acetylsulfanilyl chloride in the presence of anhydrous sodium carbonate. This procedure was adopted when it was found that the 3-chloro-4-dimethylaminocyaniline could not be isolated without extensive decomposition. The preparation

⁴Walker and Van Dyke, Proc. Soc. Exptl. Biol. Med., 45, 368 (1941); C. A., 36, 567 (1942).

⁵Coggeshall, Maier, and Best, J. Am. Med. Assoc., 117, 1077 (1941).

of the latter compound has been reported by Ayling, *et. al.*,⁶ but under circumstances which did not make the information available until some time after this work had been completed. These authors report the preparation of the compound by three independent methods, but they only report its actual isolation in one of the cases; however, in this instance they state that the compound appeared to undergo no decomposition. They also reported that the supposed compound did not give Lauth's test for p-diamines.⁷ The methods of preparation utilized by Ayling were chlorination and subsequent hydrolysis of 4-dimethylaminocetanilide, reduction of 5-nitro-4-dimethylaminocetanilide followed by a Sandmeyer reaction, and reduction of 3-chloro-4-dimethylaminonitrobenzene, but only in the first case was the isolation of the product reported. Despite this apparent anomaly there seems to be little doubt that the compound herein reported is the one claimed since the precursor nitro compound has been fully described in the literature by Ayling and van Duin,⁸ the latter of whom prepared the compound by three independent methods. The physical

⁶Ayling, Garvin, and Hinkel, *J. Chem. Soc.*, 753 (1942).

⁷Karrer, *Organic Chemistry* (New York: Elsevier Publishing Co., 1946), p. 609.

⁸van Duin, *Res. Trav. Chim.*, 376 (1932); *G. A.*, 26, 5550 (1932).

constants there reported agree with those found in this work. The difficulties encountered in the isolation of this compound may have been inherent in the method employed for its preparation, i. e. the catalytic reduction of an ether solution of the corresponding nitro compound in the presence of Raney nickel catalyst.

The preparation of the remaining sulfa type compounds was accomplished as previously reported⁹ but with a few minor changes which are fully covered in the experimental section of this thesis.

With the advent of no particularly spectacular sulfa drug there occurred a change in emphasis to aminoalcohol type compounds. The investigation of this type of compound came about largely as a result of the activity of the cinchona alkaloids and some quinoline methanols. The compounds reported here are an outgrowth of previous work done at the National Institute of Health¹⁰ and in these laboratories.¹¹

Both of the aminoalcohols described in this paper were prepared¹² from 4-(4'-bromophenyl)-phenacyl bromide by condensation with an appropriate amine followed by Meerwein-Ponndorf reduction of the ketonic product. The starting

⁹Drake, Baker, Gorman, Hamlin, Hayes, Haywood, Peck, Freston, Sterling, Van Hook, and Walton, J. Am. Chem. Soc., **66**, 1802 (1944).

¹⁰May and Mossettig, J. Org. Chem., **11**, 1 (1946).

¹¹Drake and Goldman, J. Org. Chem., **11**, 100 (1946).

¹²Drake, Gorman, Peck, and Walton, J. Org. Chem., **11** 795 (1946).

material was prepared from commercially available 4-bromo-biphenyl by Friedel-Crafts reaction with acetic anhydride and subsequent bromination of the methyl ketone. The bromo-methyl compound has not been previously reported in the literature; its proof of structure is based by analogy upon bromination of similar type compounds previously reported.^{13 14}

Although work still continued to be done in many laboratories in the study of other compounds there was now an overall change in emphasis to the quinoline type compounds themselves. The investigations were restricted chiefly to the 4-amino- and the 8-aminoquinolines. As a group the 4-aminoquinolines received the first careful attention. Not many of this type of compound had been reported in the malaria literature; some patents did indicate that both German and Russian workers^{15,16,17,18} had been sufficiently interested

¹³Drake and Bronitsky, J. Am. Chem. Soc., 52, 5715 (1930).

¹⁴Carpenter and Turner, J. Chem. Soc., 859 (1934).

¹⁵Andersog, Breitner, and Jung, German Patent 633,692 (Oct. 26, 1939); C. A., 36, 4973 (1942).

¹⁶Andersog, Breitner, and Jung, U. S. Patent 2,253,970 (Mar. 4, 1941); C. A., 35, 3771 (1941).

¹⁷Mal'perin, Sov. Parazitol. Parasitic Diseases (U.S.S.R.), 9, 44 (1940); C. A., 35, 1874 (1942).

¹⁸Magiason and Rubatov, J. Gen. Chem. (U.S.S.R.), 7, 1396 (1937); C. A., 32, 564 (1938).

to do considerable exploratory work in the field. Later work, including that obtained in this paper, has been reported in this country.

Each of the 4-aminoquinolines studied fell into one of two large classes. Either the compound in question was one made by the condensation of 4,7-dichloroquinoline with some diamine which was appropriately substituted, or it was made by the condensation of 4-amino-1-diethyleminopentane with some appropriately substituted 4-chloroquinoline. The types of compounds so prepared had then either the same nuclei with varying types of sidechains or had the same sidechains on varying nuclei.

The preparation of this type of compound followed a somewhat general pattern but one which differed usually in some details from one compound to another. The condensation reactions themselves were generally carried out on the fusion mixture of the reactants in the ratio of 2.2 moles of side-chain per mole of nucleus. The excess of the sidechain was employed to remove the hydrogen chloride formed during the coupling reaction. The reaction temperature varied widely from compound to compound and was determined in each individual case somewhat as follows. The reaction mixture was

¹⁹Steck, Hallock, and Holland, J. Am. Chem. Soc., 68, 129, 132 (1946).

²⁰Brake, Creech, Garman, Haywood, Peck, Van Hook, and Walton, J. Am. Chem. Soc., 68, 1808 (1946).

Heated very slowly after fusion was accomplished while maintaining a careful observation of the temperatures within the reaction mixture and in the external heating bath. As the region of appreciable reaction was reached the differential temperature became smaller and smaller and finally disappeared. An attempt was usually made to carry out the condensation at the temperature where the differential temperature was zero or where the reaction temperature was one to two degrees higher than that of the heating bath. In many cases, heating more strongly than this resulted in a very vigorous exothermic reaction in which the temperature of the reaction mixture often rose 50-100° higher than that of the heating bath. Such reactions usually resulted in the formation of large amounts of tarry by-products from which the desired products could be isolated only in poor yields or not at all.

In the controlled reactions the drop of the internal temperature after the reaction has proceeded for some time was taken as an indication that the major part of the condensation was completed and that the reaction would be substantially complete in another fraction of the elapsed reaction time. The actual completion of the reaction could often be determined by the application of a simple buffer test. A few drops of the reaction mixture were removed and dissolved in the smallest amount of 5% nitric acid required to effect solution and to this solution a few drops of saturated aqueous sodium acetate were added. Any unreacted 4,7-dichloroquinoline

dissolved in the nitric acid but was precipitated from the less acidic buffer. Consequently, absence of a precipitate following the addition of the sodium acetate could usually be taken as an indication that the reaction was complete. Considerable care had to be exercised in the use of this test. Some of the condensation products formed nitrates which were insoluble in the mixture, and some of the highly substituted quinoline nuclei failed to dissolve in the acid.

Of the compounds described in this paper three represent variations of the nucleus. Of the sidechain variants two are diethylaminocyclohexylamino types and the other has a diethylaminohexylamino sidechain.

The preparation of 7-chloro-4-(6'-diethylaminohexylamino)-quinoline followed, for the most part, the procedure previously described; any slight variations in procedure will be noted in the experimental section. It is interesting that the free base isolated from this reaction was impure and was purified only through the formation and recrystallization of the salt. Investigation of the source of the sidechain (prepared in this laboratory) indicated that it contained some impurity which was not removed completely even by purification of the diamine through the dithiocarbamate. The type of contaminant is not readily apparent from the nature of the synthesis used in its preparation. (The compound was prepared from bromochloropentane by reaction first with sodium cyanide and then with diethylamine followed by reduction to the amine with sodium

and alcohol in toluene.) One possible contaminant would be the 7-chloro-4-(5'-chlorohexylamino)-quinoline which would result if the reaction with diethylamine did not go to completion. The analysis of the product would indicate, however, that the impurity had been removed by the preparation and purification of the salt.

The cyclohexyl type compounds were prepared, with minor exceptions, by the methods which have already been described. 7-Chloro-4-(4'-diethylamino)cyclohexylamino)-quinoline was interesting in that it was found to consist of cis-trans isomers, as might have been expected. The isomers were separated on a small scale by an involved fractional crystallization and three constant-melting types of material were obtained. For convenience, and because such was actually suspected to be the case, these fractions were known as cis, trans, and eutectic. Depending upon the catalyst and the conditions used in the reduction step of the preparation of the sidechain from 4-diethylaminosniline the ratio of isomers in the sidechain was changed so that condensation reactions gave chiefly material having the eutectic or the trans melting point. No sidechain which gave preponderantly the cis isomer was found. Since the trans form could be isolated readily and in good yield from one type of sidechain, and since it was as active or slightly more active than the eutectic mixture originally submitted for testing, there seemed to be little point in further investigation or isolation of these isomers. During preliminary work with the Craig counter-current extraction

method²¹ of determining homogeneity these three fractions of material were examined. The findings bear out the assumptions made above as to the nature of these fractions.²² The so-called cis and trans fractions showed homogeneities of 95% and 92% respectively. The eutectic mixture was indicated to be two compounds in the proportion of 66:30; this ratio was shown to be a ratio of cis to trans.

The directions given in the experimental section are those which were used in the isolation of the various fractions from samples of sidechain secured as therein noted. It should be recognized that these methods of isolation might be totally inadequate for sidechain mixtures of a different composition. As stated above, sidechain obtained by certain procedures reacts to form good yields of the easily isolable trans form while others give a product which appears to be chiefly eutectic. The cis form can be isolated only with great difficulty.

Of the 4-aminoquinolines which are herein reported having variation of nuclear structure two are phenoxyquinolines while the other is a methoxyphenylquinoline. These compounds were all prepared by the standard methods which have been previously mentioned. The details of the experimental section will serve

²¹Craig, J. Biol. Chem., 135, 519 (1944); Craig, et. al., Ibid., 161, 521 (1945).

²²Walton, Synthetic Antimalarials (Thesis, University of Maryland, College Park, Maryland, 1948).

to indicate and describe any changes in procedure which were adopted.

Since a thorough investigation of the 4-aminoquinolines did not serve to uncover any outstanding curative or prophylactic drugs the attention of investigators turned to the 8-aminoquinoline type compounds of which group Plasmochin (Pamaquin) is a member. Plasmochin has a true curative action in cases of vivax malaria, i. e. it prevents the relapses which occur in the absence of additional infection and are known characteristics of vivax malaria. A number of compounds analogous to Plasmochin have been synthesized and shown to have considerable activity. A true causal prophylactic remains to be found. In an attempt to find such a compound considerable time has been spent in attempts to propose, and then to synthesize and test, series of compounds which may have the most desirable properties. To this end many compounds having slight or even considerable prophylactic activity have been slightly altered by addition or subtraction of groups of atoms in an effort to establish the efficacy or essentiality of these groups.

One such investigation described by this paper consisted in substituting guanyl groups for one of the hydrogens of the terminal nitrogen of a series of 8-(aminoskylamino)-5-methoxyquinolines. This substitution was carried out through the series where the alkyl portion of the sidechain varied from ethyl through amyl. Subsequent to the decision to prepare these compounds for testing there appeared information that

certain substituted guanidines, especially p-anisylguanidine nitrate, showed a definite causal prophylactic activity²³ in avian malaria. Other evidences of activity in guanidine derivatives have also been reported since this work was instituted. Curd and Rose²⁴ reported that a number of substituted phenylguanidinopyrimidines were found to have high antimalarial activity against F. gallinaceum in chicks. One of the most active of these compounds was 2-(4'-chlorophenylguanidino)-4-(2'-diethylaminoethylamino)-5-methylpyrimidine, but equivalent activity was shown when the chlorine atom was replaced by a fluorine atom or cyano or nitro group. Such information served to confirm the advisability of investigating the quinoline substituted guanidines.

The Survey of Antimalarial Drugs 1941-1945²⁵ records 78 substituted guanidines only eight of which are listed as showing activity; two of these compounds are said to have suppressive activity and six are reported to have prophylactic activity in avian malaria. Only three quinoline substituted guanidines are listed, and all of these are reported to be inactive. Other reports of inactivity in substituted guanidines have been made by May²⁵ who prepared and submitted for

²³ King and Tonkin, J. Chem. Soc., 1063 (1945).

²⁴ Curd and Rose, J. Chem. Soc., 362 (1946).

²⁵ May, J. Org. Chem., 12, 437 (1947).

testing some guanidine derivatives of 9-phenanthrylamine. These compounds were found inactive against Gallinaceum malaria in chicks.

Much work has been done on the introduction of the guanidino group into various types of molecules by a number of different reactions, and mention will be made of those which influenced the course of this research either from the standpoint of the type of compound prepared or of the method used.

Werner and Bell²⁵ reported the preparation of N-alkyl- and N-dialkyl-guanidines by the fusion of the corresponding alkyl- and dialkylamines hydrochlorides with dicyandiamide. The alkyl groups in this case were ethyl and methyl, but no reference to the use of this method for complex molecules has been found.

The preparation of guanidines from an amine salt and cyanamide in aqueous or alcoholic solution has been reported in a number of instances.^{25,26,27,28}

The fusion of guanidine salts, such as guanidine thiocyanate, with amines has also been reported to give satis-

²⁵Werner and Bell, J. Chem. Soc., 181, 1790 (1923).

²⁷Chemische Fabrik auf Aktien vorm. E. Schering, British Patent 279, 864, Oct. 26, 1926; Q. A., 22, 2951 (1928).

²⁸Braun, J. Am. Chem. Soc., 55, 1250 (1933).

factory yields of guanidine derivatives. 29, 30, 31

The reaction of an amine in water, alcohol, or a mixed solvent with S-methyl-isothiourea sulfate or with other S-alkyl-isothiourea salts has been used extensively in the preparation of guanidine derivatives. 23, 28, 32, 33, 34, 35, 36

The guanidine derivatives described were all prepared in the same general manner from the corresponding S-(amino-alkylamino)-6-methoxyquinoline and S-methyl-isothiourea sulfate. Considerable difficulty was experienced in the purification of the products. It was found possible to precipitate a carbonate of the product from organic solvents which were slightly wet without precipitating the starting materials. The carbonates so obtained were not found to be

²⁹ von Sodin, German Patent 522,057 (July 10, 1929);
C.A., 25, 3013 (1931).

³⁰ Prochnow, U. S. Patent 2,007,770 (July 9, 1935);
C.A., 29, 5993 (1935).

³¹ Reichel, German Patent 637,740 (Nov. 3, 1936); C. A.,
31, 2752 (1937).

³² Phillips and Clarke, J. Am. Chem. Soc., 45, 1755 (1923).

³³ Chemische Fabrik auf Aktien, vorm. K. Schering, British
Patent 282,133 (Nov. 30, 1925); C.A., 21, 3625 (1926).

³⁴ Schering-Kohlbaum, German Patent 465,579 (Aug. 5, 1925);
C.A., 23, 1649 (1929); and German Patent 465,576 (July 12, 1925);
C.A., 22, 4131 (1928).

³⁵ Smith, J. Am. Chem. Soc., 51, 476 (1929).

³⁶ Buck, Baitay, and Perry, J. Am. Chem. Soc., 64, 2251 (1942).

of simple stoichiometric composition but were possibly a mixture of carbonate and bicarbonate; they could be isolated and dried but were not stable on standing even in an inert atmosphere; they could not be recrystallized. As a consequence of these facts it was found most convenient to precipitate the solid carbonate, separate it by filtration, wash it with ether, and dry it rapidly in vacuo. This solid was dissolved in alcohol and titrated with alcoholic hydrogen chloride. The titration method was adopted as a convenient means of adding approximately two equivalents of acid. The titration can be accomplished with considerable accuracy since the monobasic salts of these compounds are essentially colorless while the dibasic salts are usually bright yellow, orange, or red. The color change can be easily observed if an aliquot of the solid is used for the titration while it is dissolved in approximately the amount of alcohol to be used for the total sample. The addition of one equivalent of acid to this solution does not change its color appreciably, but a sharp change in color can be noted at this point upon addition of one or two drops of relatively dilute acid. The ease of this process and the ease of subsequent isolation of the hydrochlorides prompted the conversion of all these guanidines to the hydrochlorides, however, after all had been converted to the hydrochlorides in this manner it was found that these salts showed a remarkable tendency to hydrate

and, for convenience, a salt was sought which might be recrystallized in the presence of at least small amounts of water without hydration. It was found that the nitrates behaved much more satisfactorily in this respect. The hydrochlorides were, as a result, all transposed to the nitrates by recrystallization from relatively concentrated solutions of ammonium nitrate. Two or three recrystallizations usually sufficed to yield a product which did not give a test for chloride ion. These crystallizations, which were accomplished by dissolving the salt in a small amount of water and adding an excess of 30% ammonium nitrate, were carried out in very good yields.

The nitrate salts were found to be only slightly soluble in absolute and even in ordinary ethanol. In some cases the compounds could be recrystallized by dissolving them in large volumes of absolute ethanol and then concentrating the solution to a point where it was highly supersaturated. A more effective and less time-consuming process was found to consist of dissolving the compound in a small amount of water and diluting the resultant solution with absolute ethanol. This alcoholic solution could then be concentrated, in which process the amount of water present was considerably reduced. The compounds so recrystallized showed no evidence of hydration.

All of the substituted guanidines prepared have been

found to give the Sakaguchi³⁷ test for monoalkylguanidines. Slight modifications of the method were utilized in certain instances, and a typical test procedure will be described in the experimental section.

The Sakaguchi test has been investigated rather thoroughly by Poller³⁸ with regard to Sakaguchi's claim that the test was specific for monoalkylguanidines. Poller found that the test is not given by N^1 , N^1 -dialkylguanidines or by N^1 , N^3 -dialkylguanidines but that it is positive for some N^1 , N^3 -dialkylguanidines.

Fearson³⁹ has developed a similar test which differs from the Sakaguchi test in that thymol is substituted for alpha-naphthol. He found by extensive investigation that this test is subject to the same limitations of alkylation as is the Sakaguchi test.

On the basis of this evidence it is assumed that the guanyl groups added were introduced at the terminal nitrogen of the sidechain rather than at the initial aromatic nitrogen. Further qualitative evidence for this assumption is afforded by the facts that the compounds prepared show a tendency to form dibasic salts (rather than the tribasic salts which would be expected of the alternative product) and that the more reactive terminal amino group would be expected to

³⁷Sakaguchi, J. Biochem. (Japan), 5, 135 (1926); C.A., 20, 925 (1926).

³⁸Poller, Exp., 59, 1927 (1926).

³⁹Fearson, Sci. Proc. Roy. Dublin Soc., EE, 415 (1941); C. A., 35, 7319 (1941).

undergo preferential reaction. However, it must be recognized that there exists the possibility that the alternative product was obtained.

The 8-(aminoalkylamino)-6-methoxyquinolines which served as the starting materials for these guanidines have all been previously prepared and reported in the literature,^{40,41,42,43,44} The preparative details for these compounds were inserted in this thesis when one of the following conditions was met: 1) the compound was prepared in better yield due to some change in the experimental procedure, 2) the compound was prepared in approximately equivalent yield but in significantly purer form as indicated by physical constants, 3) the compound was prepared in equivalent or slightly lower yield but by a method deemed to be superior from the time or the manipulative standpoint, or 4) certain changes in procedure were attempted which emphatically failed to improve on existing directions. The intermediates used in the preparation of these starting materials are also known compounds. References to their preparation will be given in the experimental section only when they meet one of the conditions set down above.

⁴⁰Baldwin, J. Chem. Soc., 2959 (1929).

⁴¹Beer, J. Gen. Chem. (U.S.S.R.), 9, 2138 (1939); C.A., 34, 4148 (1940).

⁴²Kissinger, Von, and Carmack, J. Am. Chem. Soc., 68, 1863 (1946).

⁴³Mooser, J. Am. Chem. Soc., 66, 1865 (1944).

⁴⁴Quin and Robinson, J. Chem. Soc., 355 (1943).

An attempt was made to prepare the 8-(3'-aminoalkylamino)-6-methoxyquinoline in a way not previously reported. The general plan of this attempt was first to prepare the corresponding hydroxyalkylamino-quinoline and replace its hydroxyl group with a halogen; the halogen could be then replaced by an amine group with sodamide or ammonia. The hydroxyl compound was easily prepared, is a new compound, and is reported in the experimental section. Attempts to prepare the bromo or chloro compounds were uniformly unsuccessful. The method of Yanko, et. al.,⁴⁵ which had been used for the corresponding propyl compounds, failed to give any identifiable products. The reaction of the hydroxyl compound with thionyl chloride appeared to proceed readily even at low temperatures, however, neither the desired product nor any other identified product could be obtained. It was assumed that the halide formed cyclized readily even under the mild conditions employed. This assumption was corroborated by Lee⁴⁶ who isolated 6-methoxy-8-(N-piperidino)-quinoline from this same reaction.

Since it has been generally shown that 8-(alkylaminoalkylamino)- and dialkylaminoalkylaminoquinolines are better anti-malarials than the corresponding aminoalkylaminoquinolines

⁴⁵Yanko, Mosher, and Whitmore, J. Am. Chem. Soc., 57, 664 (1945).

⁴⁶Lee, Synthesis of Chemotherapeutic Agents (Thesis, Magdalen College, Oxford University, London, England, 1946).

an attempt was made to prepare some alkylguanidinoalkyl-aminequinolines corresponding to the guanidoalkylaminoquinolines which have been prepared. The choice of the isopropyl group as the terminal alkyl group was dictated largely by the fact that the isopropyl group is the terminal sidechain group of two of the most important antimalarials resulting from the synthetic program, Fentaquin, (C^N 15,296), 8-(5'-isopropylaminosaxylamino)-6-methoxyquinoline phosphate,⁴⁷ and Paludrine, (SM-12,637), N¹-(4'-chlorophenyl)-N³-isopropylbiguanide.

In view of the ease of preparation of the N¹-monoalkylguanidines previously described it was determined to attempt the preparation of the N³-isopropyl derivatives in a similar way using N-isopropyl-S-methyl-isothiourea in place of the S-methyl-isothiourea. The obvious method of methylating isopropylthiourea to prepare the desired isothiourea, a compound which has not previously been reported, led in the case of methylation with either methyl sulfate or methyl iodide to the formation of a syrup from which the only crystalline material obtained was small amounts of unreacted isopropylthiourea. However, from this syrup a picrate of the desired product could be prepared in good yield. Reaction of the picrate with amines led to the liberation of methyl mercaptan suggesting that S-alkylation had been

⁴⁷Brake, Van Hook, German, Hayes, Johnson, Kelley, Melamed, and Peck, J. Am. Chem. Soc., 68, 1529 (1946).

accomplished. Attempts to use the reaction between this picrate and the aminoalkylaminoquinolines to prepare the desired isopropyl substituted guanidines were unsuccessful. These reactions proceeded with the elimination of methyl mercaptan which might indicate that the desired reaction was taking place. The failure to isolate a product would indicate that either the reaction did not proceed as anticipated, that some subsequent reaction altered the nature of the product, or that the proper method of isolation had not been employed. Since the failure of this reaction may have been due to the use of the picrate a further attempt to prepare the desired compound was made using the syrup which resulted from the methylation reaction. As in the case of the picrate methyl mercaptan was evolved, but again no product could be isolated.

Several other approaches to this compound were also investigated. For example, reaction of 6-(5'-aminoamylamine)-6-methoxyquinoline with isopropyl isothiocyanate should lead to 1-(5-(6-methoxy-8-quinolyamine)-amyl)-5-isopropylthiourea. This compound might be expected to be 8-alkylated with an alkyl halide or a dialkyl sulfate, and the resultant isothiourea might then be desulfurized with ammonia. When this method was attempted both of the expected reactions seemed to proceed even though no crystalline compounds could be isolated. The final product did not, however, liberate methyl mercaptan

when treated with an amine or even when boiled with aqueous sodium hydroxide. This would indicate that even if alkylation had been accomplished it was not alkylation on sulfur; because of this fact this method was not further investigated.

The final method investigated for the preparation of the isopropyl substituted guanidine was the reaction between a salt of 6-(5'-aminoamylamino)-6-methoxyquinoline and isopropyl cyanamide. This method was considered inasmuch as isopropyl cyanamide might be made by the method of Pierron⁴⁵ or Berger⁴⁹, both of which would utilize isopropylthiourea, which had already been prepared, as the starting material. However, although these methods are apparently very effective for the preparation of the monoaryl derivatives of cyanamide, they are not suitable for the preparation of the lower aliphatic cyanamides. From these reactions, instead of the desired isopropyl cyanamide, there was obtained a good yield of isopropyl urea.

The attempted preparation of compounds which incorporated the biguanide group into a substituted quinoline molecule is a logical consequence of a study of previously reported active antimalarial agents. Curd and Rose⁵⁰ prepared a series of

⁴⁵Pierron, Ann. Chim., 15, 163 (1908).

⁴⁹Berger, Monatsh., 3, 219 (1884).

⁵⁰Curd and Rose, J. Chem. Soc., 729 (1946).

biguanides because of their open-chain relationship to a series of diaminopyrimidines which they had found to have considerable antimalarial activity. A number of the biguanides reported by Gard and Rose were found to have activity of a high order and have been clinically tested in human malaria. One of these compounds, N¹-(4'-chlorophenyl)-N⁵-isopropyl-biguanide, to which the name Faludrine has been assigned, has proved to be quite effective and is in commercial production as an antimalarial.

Other biguanides, some of which show activity, have been reported by King and Tonkin⁵¹, and some which were without exception inactive have been reported by May.^{51, 51}

The preparative methods for biguanides have been studied in some detail utilizing as a starting material in most cases the compound dicyandiamide which was found by Bamberger and Dieckmann⁵² to react with ammonium chloride to yield biguanide hydrochloride. The reaction was later extended to aliphatic and aromatic amines by Smolke and Friedreich⁵³ and Slotta and Techesche.⁵⁴ It was found that the use of ammoniacal copper

⁵¹May, J. Org. Chem., 12, 443 (1947).

⁵²Bamberger and Dieckmann, Ber., 25, 345 (1892).

⁵³Smolke and Friedreich, Monatsh., 9, 283 (1878).

⁵⁴Slotta and Techesche, Ber., 62, 1394 (1929).

sulfate solution aided the reaction of ammonia with dicyandiamide,⁵⁵ and the use of this method has been extended to aliphatic and aromatic amines by Curd and Rose.⁵⁹ The use of copper sulfate was found to aid in the isolation of the biguanide since a sparingly soluble copper complex was formed.

The attempted condensations of the dihydrochlorides of the various 3-(alkylalkylamino)-6-methoxyguinolines failed to produce any of the desired products. The only identifiable material isolated from these reactions were the monobasic salts of the starting bases. Since these salts have not been previously reported they will be described in the experimental section.

The method described by Curd and Rose⁵⁹ for aliphatic amines was also tried without success, however, it is believed that a careful study of this reaction and the method of isolation of the product would suffice to make the preparation of these compounds possible.

⁵⁵Bathke, Ber., 12, 780 (1879); Herth, Ber., 12 (1890); and Hackman, Ann., 376, 170 (1910).

EXPERIMENTAL

The author wishes to express his appreciation to Miss Eleanor Werble, Mrs. Mary Albridge, Mr. Byron Baer, and Mr. J. Daniel Draper for the micro and semi-micro analyses reported in this thesis.

2-Chloro-4-nitro-N,N-dimethylaniline.⁵⁶ - This compound was prepared from 4-nitro-N,N-dimethylaniline⁵⁷ by direct chlorination in concentrated hydrochloric acid and glacial acetic acid at ice-bath temperature.

A solution of 81 g. (0.5 mole) of 4-nitro-N,N-dimethylaniline in 125 ml. of glacial acetic acid and 250 ml. of concentrated hydrochloric acid was vigorously stirred at ice-bath temperature while a stream of chlorine gas was blown over the surface. The reaction was assumed to be completed

⁵⁶ This compound had been previously prepared by Ayling, et. al.,⁶ by chlorination in chloroform at room temperature. They report a 75% yield of a product melting at 78°. As previously noted this reference was not available at the time this compound was prepared, and, since the method is somewhat different and the yield better, it is reported here in detail.

⁵⁷

4-Nitro-N,N-dimethylaniline is commercially available. However, that used in this instance was prepared from 4-chloronitrobenzene by amination with anhydrous dimethylamine in a steel bomb at 170° for two and one-half hours. It was found possible to use a 50% solution of dimethylamine in water to prepare the compound in equivalent yields (85-90%) if the reaction time was increased to six hours. This amination procedure is essentially that of Mills. (Mills, to Dow Chemical Co., U. S. Patent 1,935,815 (Nov. 14, 1933); C. A., 28, p 485 (1934).

when one equivalent of chlorine had been absorbed. The reaction mixture was then poured over cracked ice and neutralized with sodium hydroxide taking care that the temperature did not rise above 10° during this step. When neutralization had been accomplished, the solid was removed by filtration and washed with water; it was then recrystallized to constant melting point of 76-77°. There was obtained 80 g. (82%) of product.

3-Chloro-6-azine-N,N-dimethylaniline.⁵⁸ - A solution of 15 g. (0.075 mole) of 2-chloro-4-nitro-N,N-dimethylaniline in the minimum amount of ether required to dissolve it was added to approximately 3 g. of Raney nickel catalyst, which had previously been saturated with hydrogen, and the resultant mixture was shaken with hydrogen at low pressure (initial pressure 40-50 p. s. i.) until the theoretical amount of hydrogen had been absorbed. All attempts to isolate this compound resulted in its extensive decomposition. Attempts were made to handle the compound under an inert atmosphere during isolation and/or preparation of a salt. These attempts met uniformly with failure. The catalyst was, as a result, removed by filtration and the ether solution was used directly in the preparation of N-acetylsulfanilamide-3-chloro-4-dimethylaminobenzene.

N-Acetylsulfanilamide-3-chloro-4-dimethylaminobenzene.

⁵⁸Prepared by Ayling, et. al., (see 6) by stannous chloride reduction of the corresponding nitro compound.

The ether solution of 2-chloro-4-amino-N,N-dimethylaminoaniline prepared above was placed in a flask equipped with an efficient reflux condenser and provisions for the passage of a stream of nitrogen over the surface of the solution. There was then added 18 g. (0.077 mole) of N-acetylsulfanilyl chloride and 4.08 g. (0.0385 mole) of anhydrous sodium carbonate. This mixture was thoroughly stirred and refluxed for one and one-half hours. The reaction mixture was poured over cracked ice, and the organic layer was separated. The solid resulting from the evaporation of the ether layer was recrystallized to constant melting point from ethanol to yield 15 g. (48%) of material which melted at 127-128°.

2'-Chloro-4'-dimethylamino-sulfanilanilide (95-5059; UM 17). - A mixture of 3 g. (0.0214 mole) of N-acetylsulfanilamide-2-chloro-4-dimethylaminobenzene and 100 ml. of 10% hydrochloric acid was heated under reflux for 30 minutes. The reaction mixture was cooled to ice-bath temperature and neutralized with 10% sodium hydroxide solution. The resultant solid was removed by filtration and dried; it was then dissolved in just enough ethanol to effect solution and treated with 2 g. of H_2O_2 . The decolorized solution was cooled rapidly in an ice-bath and decanted from a small amount of oil which separated. The supernatant liquid on standing deposited 2.5 g. (50%) of white crystals which melted at

101-105.5°. Further attempts to purify this material by recrystallization caused apparent decomposition as shown by a lowering and broadening of the melting point range. Anal.
Calcd. for $C_{14}H_{10}ClN_2O_2$: C, 51.51; H, 4.95; Cl, 10.88;
N, 12.90. Found: C, 51.60, 51.41; H, 5.31, 5.15; Cl, 10.85,
10.97; N, 12.85, 13.00.⁵⁹

5-Bromo-1-nitronaphthalene.⁶⁰ - To 30 g. (0.29 mole) of 1-nitronaphthalene was added 1 g. of ferric chloride and the resultant mixture was warmed in a water bath until the nitronaphthalene had melted (ca. 60-65°). The external heating was then discontinued and 46.25 g. (0.29 mole) of bromine was added at the rate of approximately ten drops per minute. The exothermic reaction which took place was sufficient to maintain the temperature of the mixture. After the bromine had been added, stirring was continued until the reaction mixture solidified. The reaction flask was then immersed in an oil bath at 150° and a rapid stream of steam was blown through the molten reaction mixture. The distillate consisted chiefly of unreacted nitronaphthalene. The molten residue was

⁵⁹Attempts to use alkaline hydrolysis yielded an oil which could not be crystallized. Other solvents than ethanol were investigated but despite the obvious disadvantages of the latter nothing superior was found.

⁶⁰This material was prepared by a modification of the method of McLeish and Campbell, J. Chem. Soc., 1105 (1937), which was in turn a modification of the method of Scheufelin Ann., 251, 185 (1905). These methods differed chiefly in the manner in which the product was worked up. The yield reported below is better than had previously been reported.

poured into water and the solid so formed was removed by filtration. This solid was dissolved in alcohol, treated with decolorizing carbon, and then allowed to crystallize slowly. There was obtained 25 g. of material which melted at 114-117°. After two recrystallizations from ethanol there remained 15.6 g. (38%); the purified product melted at 119-122°.

5-Bromo-1-naphthylamine hydrobromide.⁶¹ - A solution of 23.4 g. (0.114 mole) of 5-bromo-1-nitronaphthalene in 150 ml. of benzene was added to approximately 5 g. of Raney nickel catalyst which had previously been saturated with hydrogen. This mixture was then shaken with hydrogen at low pressure (initial pressure 40-50 p. s. i.) until the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate stirred and cooled while a stream of anhydrous hydrogen bromide was blown across its surface until a slight excess of hydrogen bromide could be detected. The solid was then removed by filtration, washed thoroughly with dry ether, and dried. There was obtained 25.7 g. (64%) of hydrobromide which was used directly in the next step.

1-Acetylsulfanilamide-5-bromonaphthalene. - A solution of 22.5 g. (0.074 mole) of 5-bromo-1-naphthylamine hydro-

⁶¹This amine had previously been prepared by Ellmann, Ber. 35, 2804 (1902), by reduction of the 5-bromo-1-nitronaphthalene with stannous chloride.

bromide and 17.4 g. (0.0745 mole) of N-acetyl-sulfanilyl chloride in 150 ml. of pyridine was stirred and heated at 70° for two and one-half hours. The reaction mixture was poured with vigorous stirring on a mixture of finely cracked ice and 150 ml. of concentrated hydrochloric acid. The colored solid so precipitated was removed by filtration and dried. The dried solid was slurred with 150 ml. of refluxing ethanol; the mixture was then cooled and the solid removed by filtration. The product so obtained when dried weighed 32 g. and was used directly in the next step.

N¹-(5-bromo-1-naphthyl)-sulfanilamide (SK-7187; UM 80). -

To a mixture of 35 g. (0.09 mole) of 1-acetylsulfanilamido-5-bromonaphthalene and 150 ml. of diethylene glycol was added 35 ml. of 1:1 hydrochloric acid (17-19%) and the mixture was heated under reflux until solution was complete, whereupon it was poured into 600 ml. of water and the acid was neutralized carefully by the addition of 10% sodium hydroxide solution. The addition of sodium hydroxide was then continued until the precipitate first formed by the neutralization had again completely dissolved. The product was then reprecipitated by neutralization with acid, removed by filtration, and dried.

After recrystallization from ethanol the substance weighed 24.7 g. (88%); it melted at 116-117°. Anal. Calc'd for C₁₆H₁₃BrN₂O₂S: C, 50.95; H, 3.44. Found: C, 50.03, 51.38; H, 3.46, 3.54.

5-Nitroquinoline. - This compound was prepared according to the directions of Fieser and Hershberg⁶² with the following exceptions. In the formation of the quinoline sulfate only one equivalent of sulfuric acid was used because it was found that the dry sulfate which then resulted was easier to handle than the partially dissolved material which resulted when the amount specified in the article was used. Also, instead of the 65% fuming sulfuric acid recommended, 20% fuming acid was used. The yields were about 27% (8% lower than reported in the reference).

5-Aminoquinoline dihydrochloride.⁶³ - A solution of 20 g. (0.115 mole) of 5-nitroquinoline in sufficient methyl alcohol to effect solution was heated under reflux for about twenty minutes with one gram of Raney nickel catalyst;⁶⁴ the catalyst was removed by filtration and the solution was poured on ca. 5 g. of Raney nickel which had previously been saturated

⁶²Fieser and Hershberg, J. Am. Chem. Soc., **62**, 1640 (1940).

⁶³This amine has been prepared by Duffen, J. Chem. Soc., 783 (1892), and by Dikshoorn, Rec. trav. chim., **48**, 147 (1829), who reduced the nitro compound by means of stannous chloride, and by Keurmann, Ber., **50**, 1627 (1917), who accomplished the reduction of the nitro compound with iron and acetic acid. It has also been prepared by catalytic hydrogenation by Fieser and Hershberg, J. Am. Chem. Soc., **62**, 1640 (1940), who used Adams platinum catalyst and by Winterbottom, Ibid., 160 (1940).

⁶⁴This operation was found to be necessary to remove some poison present either in the solvent or in the nitroquinoline. The omission of this step caused the reduction to be very slow and incomplete.

with hydrogen, and the mixture was shaken with hydrogen at low pressure until the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration, and the filtrate was saturated with hydrogen chloride with cooling and stirring. The rust-colored crystalline product when dried weighed 20 g. (80%) and had a melting point of 330-340°. It was used directly in the next step without further purification.

5-Acetylsulfanilamidoquinoline.⁶⁵ - A solution of 20 g. (0.092 mole) of 5-aminoquinoline dihydrochloride and 23 g. (0.092 mole) of N-acetyl-sulfanilyl chloride in 60 ml. of pyridine was stirred at 60-70° for three hours. The reaction mixture was then poured into ice water and allowed to stand until the oil which first formed crystallized. The solid was removed by filtration and dissolved in 10% sodium hydroxide solution. This basic solution was treated with Norit; after removal of the decolorizing carbon the solution was neutralized with 10% hydrochloric acid. The solid so formed was removed by filtration and dried to yield 25.3 g. (74%) of crude material which was used directly in the next step.

N¹-(5-quinolyl)-sulfanilamide (SN-6412; UM 59).⁶⁵ - A solution of 25.3 g. (0.068 mole) of crude 5-acetylsulfanilamidoquinoline in 25 ml. of 10% hydrochloric acid and 10 ml.

⁶⁵Prepared previously by Winterbottom (see 63) and by Kobranaki, Arch. Pharm., 277, 73 (1932).

of ethanol was heated at reflux for two hours. At the end of this time 50 ml. of water was added and the solution was treated with Darco and filtered. The solution was neutralized and the precipitate formed was dissolved in 10% sodium hydroxide solution and treated with Norit. The solid was again precipitated and carried through the same procedure of treatment with decolorizing carbons in acid and basic solutions. The material which was finally precipitated was recrystallized from absolute methanol. There was obtained 2.7 g. (40%) of product which melted at 250-251°. Anal. Calc'd. for $C_{15}H_{13}NO_2$: C, 60.20; H, 4.34. Found: C, 60.5, 60.4; H, 4.62, 4.78.

4-(4'-bromophenyl)-acetophenone,⁶⁵ - sixty grams (0.45 mole) of aluminum chloride was dissolved in 300 ml. of purified nitrobenzene and the solution was cooled in an ice bath. To the cooled solution was added 40 g. (0.25 mole) of 4-bromobiphenyl, and then with vigorous stirring and cooling there was added dropwise 20 g. (0.196 mole) of acetic anhydride. After the addition was complete, the stirring was continued at ice bath temperature for one and one-half hours. The reaction mixture was then allowed to come gradually to room temperature and was then heated at 35° for three hours. The reaction mixture was poured on finely cracked ice to which had been added 100 ml.

⁶⁵ This compound has also been prepared by Carpenter and Turner, J. Chem. Soc., 669 (1924), by reaction of 4-bromobiphenyl with acetyl chloride in carbon disulfide in the presence of anhydrous aluminum chloride. They obtained a product melting 131°.

of concentrated hydrochloric acid. The ice used was sufficient to keep the temperature below 15° during the decomposition of the complex. The nitrobenzene was removed from this mixture by steam distillation, and the residue was allowed to cool. The solid material which formed during this process was removed by filtration and dried. This solid could be separated readily into fractions consisting of product and starting material. The product weighed 86.5 g. (80%, based on starting material not recovered) and melted at 127-128°.

4-(4'-bromophenyl)-phenacyl bromide. - A mixture of 126 g. (0.450 mole) of 4-(4'-bromophenyl)-acetophenone in 1000 ml. of glacial acetic acid was heated slowly until the solid had completely dissolved. To this solution 98 g. (0.55 mole) of bromine was added with continued stirring. The mixture was stirred for twenty minutes after the addition of bromine had been completed and was then cooled in an ice bath. The solid was removed by filtration and combined with a further crop of material obtained by dilution of the filtrate with water. The combined solids were recrystallized from toluene to yield 86.5 g. (82%) of material which melted at 141-144°. (This yield could be considerably improved by working up the filtrates from the recrystallization.) The material was used in this state of purity for the next step.

α -Di-n-butylamino-4-(4'-bromophenyl)-acetophenone hydrochloride. - A solution of 25 g. (0.070 mole) of 4-(4'-bromo-

phenyl)-phenacyl bromide and 19.6 g. (0.162 mole) of di-*n*-butylamine in 500 ml. of anhydrous ether was stirred at room temperature for 24 hours. At the end of this time the di-*n*-butylamine hydrobromide was removed by filtration and a stream of anhydrous hydrogen chloride was blown across the surface of the filtrate with stirring and cooling. When a slight excess of hydrogen chloride could be detected, the solid was removed by filtration and washed carefully with anhydrous ether. This ether-wet solid was used directly in the next step.

α -(4'-Bromo-4-biphenyl)- β -diethylaminoethanol hydrochloride (SN-5851-4; UK 19). - The slightly ether-wet ω -di-*n*-butylamino-4-(4'-bromophenyl)-acetophenone hydrochloride from the previous step (which theoretically would amount to 31 g. (0.070 mole) was dissolved in 230 ml. of anhydrous isopropyl alcohol. To this solution was added 40 g. (0.196 mole) of aluminum isopropoxide⁶⁷ and the solvent was slowly distilled until a test portion taken after one hour at total reflux failed to give a test for acetone with 2,4-dinitrophenylhydrazine reagent.⁶⁸ The reaction mixture was then

⁶⁷ The aluminum isopropoxide was prepared according to the directions of Young, Hartung, and Crossley, *J. Am. Chem. Soc.*, **53**, 100 (1931).

⁶⁸ This reagent was prepared according to the directions in Shriner and Fuson, Identification of Organic Compounds (New York: John Wiley & Sons, Inc., 1940) Second Edition, p. 65.

poured with stirring on a mixture of 500 ml. of concentrated hydrochloric acid and finely cracked ice. The crystalline material so formed was removed by filtration and recrystallized from alcohol and ether. There was obtained 18 g. (58%, based upon the 4-(4'-bromophenyl)-phenacyl bromide used in the previous step) of material which melted at 170.8-171.4°. Anal. Calc'd. for $C_{22}H_{30}BrNO \cdot HCl$: C, 60.00; H, 7.04. Found: C, 59.04, 59.52; H, 6.55, 6.45.

ω -Diethylamino-4-(4'-bromophenyl)-acetophenone hydrochloride. - This compound was prepared in exactly the same manner as ω -di-n-butylamino-4-(4'-bromophenyl)-acetophenone hydrochloride using 52 g. (0.146 mole) of 4-(4'-bromophenyl)-phenacyl bromide and 85.6 g. (0.324 mole) of diethylamine in 500 ml. of anhydrous ether.

α -(4-Bromo-4-biphenyl)- β -diethylaminoethanol hydrobromide (AN-6529-13; UN 20). - This compound was prepared in the manner described for the butyl compound with the exceptions noted below. To recover all of the product it was necessary to neutralize some of the excess acid in the step following the Meerwein-Fenndorf reduction. There was obtained at this point 50 g. (80%, based on the 4-(4'-bromophenyl)-phenacyl bromide) of a slightly impure hydrochloride. This salt could not be purified sufficiently, so a portion was converted to the hydrobromide (in 87% yield), and the latter compound was recrystallized from alcohol and ether to a constant melting point of 195-195°. Anal. Calc'd. for $C_{18}H_{22}BrNO$

NBr: C, 50.34; H, 3.36; Br, 19.06. Found: C, 50.33, 50.76; H, 5.60, 5.55; Br, 18.70, 18.96, 18.77, 18.92.

4-(1'-Diethylamino-4'-pyrrolidino)-6-methoxy-3-phenylquinoline. - To 35 g. (0.129 mole) of 4-chloro-6-methoxy-3-phenylquinoline⁶⁹ was added 40.1 g. (0.254 mole) of purified 4-amino-1-diethylaminopentane⁷⁰ and the mixture was heated with stirring at 300° for eight hours. The reaction mixture was dissolved in 150 ml. of 50% acetic acid⁷¹ and then made alkaline by the addition of aqueous sodium hydroxide. The free base was then extracted with benzene, the benzene was removed by distillation, and the residue was distilled at reduced pressure. A fraction weighing 27 g. (53%) and boiling at 245° (bath 255-265°) at less than 0.5 mm. was assumed to be the product.

4-(1'-Diethylamino-4'-pyrrolidino)-6-methoxy-3-phenylquinoline Triphosphate (SN-1,905; UM 47 g). - To 24 g. (0.061 mole) of the free base was added 14.1 g. (0.122 mole) of 85% phos-

⁶⁹ Supplied by E. G. Elderfield, see J. Am. Chem. Soc., 68, 1275 (1946).

⁷⁰ All of the 4-amino-1-diethylaminopentane (hereafter called Meval diamine) used in the preparation of these drugs was first purified according to the directions of Jones, Ind. Eng. Chem., 16, 431 (1944).

⁷¹ This procedure was originally adopted because it was a convenient method of transferring the viscous product. It was later found to be more expedient to use ether for this purpose.

phoric acid and 90 ml. of water. When solution was complete there was added 40ml. of methanol and sufficient isopropyl alcohol to cause turbidity. The mixture was then sealed at 5° for four hours and the solid formed was removed by filtration and washed with 150 ml. portions of isopropyl alcohol, isopropyl alcohol--ethyl ether (1:1), and ethyl ether. This solid when dried weighed 20 g. (46%)⁷⁸ and melted at 204.5-206.0°. Anal. Calc'd. for $C_{23}H_{33}N_3O \cdot 3 K_3PO_4$: P, 15.56. Found: P, 15.50, 15.41.

4-(1'-Diethylamino-4'-pyridamino-6-phenoxyquinoline (2N-10,939; UM 59). - To 51.2 g. (0.2 mole) of 4-chloro-6-phenoxyquinoline⁷⁸ was added 69.5 g. (0.44 mole) of N-ethyl diamine and the mixture was heated at 175-180° with stirring for seven hours. The reaction mixture was treated with 200 ml. of ethyl ether and 100 ml. of 20% sodium hydroxide solution. The layers were intimately mixed and then were separated. The water layer was extracted with fresh ether and the ether extracts were then combined and dried over potassium hydroxide pellets. The ether was removed by distillation and the residue distilled at reduced pressure to yield a fraction boiling at

⁷⁸ Since most of these tribasic compounds formed dibasic salts preferentially the amount of phosphoric acid used was calculated for a dibasic salt. The use of three moles of acid per mole of base would undoubtedly have increased the yield of this compound.

⁷⁸ Supplied by Dr. B. Riegel, Northwestern University, see J. Am. Chem. Soc., 68, 1264 (1946).

345-349° (bath ca. 275°) at less than 0.5 mm. which weighed 46.2 g. (62%). This free base was recrystallized from benzene and petroleum ether to yield a crystalline material which melted at 109.5-110.5°. Anal. Calc'd. for $C_{24}H_{31}N_3O$: C, 76.56; H, 8.28. Found: C, 76.56, 76.66; H, 8.42, 8.69.

7-Chloro-4-(1'-diethylamino-6'-hexylamino)-quinoline. -

To 28.8 g. (0.145 mole) of 4,7-dichloroquinoline⁷⁴ was added 80 g. (0.89 mole) of 1-diethylamino-6-aminohexane and the mixture was heated at 145° for four hours. The reaction mixture was worked up by the addition of ethyl ether and sodium hydroxide solution as previously described. After drying the ether solution the ether was removed by distillation and the residue distilled under reduced pressure. A fraction which weighed 45.3 g. (90%) and boiled at 250-251° (bath 205-200°) at less than 0.5 mm. was assumed to be the product. Recrystallization of this oil from benzene and petroleum ether (50-50°) yielded a solid which melted in the range 65-67°. This material appeared inhomogeneous on visual examination. Melting points on a heated stage observed by a microscope indicated that there were two types of material present, one, in the form of platelets, melted at 71-73°, the other in the form of needles melted at 65-65°. The mixture of materials did not give a correct analysis. Purification was accom-

⁷⁴All 4,7-dichloroquinoline used was supplied by the University of Illinois and was purified at the University of Maryland by distillation and recrystallization from methanol.

plished by preparation of the diposphate as recorded below.

7-Chloro-4-(1'-diethylamino-3'-hexylamino)-quinoline

Diphosphate (SM-9,776-5; UM 54 g). - To 16.5 g. (0.058 mole) of the free base above dissolved in 250 ml. of boiling ethyl alcohol was added 11.4 g. (0.116 mole) of 85% phosphoric acid. The solution was stirred and heated at reflux overnight during which time some of the salt crystallized. The reaction mixture was cooled and the solid removed by filtration and dried. There was obtained 24.5 g. (94%) of product which melted at 152-157° with softening at 150°; this material was dissolved in the smallest amount of water required, diluted to turbidity with ethanol, seeded and cooled. The crystals formed were removed by filtration and dried to yield 22.2 g. (85%) of salt which melted at 200.2-201.9° after partially melting at 150° and 150° and resolidifying each time. This type of melting behavior was noted on other samples of this compound made in the same way. Anal. Calc'd. for $C_{22}H_{38}ClN_2 \cdot 2 H_3PO_4$: P, 11.70. Found: P, 11.70.

4-(1'-Diethylamino-4'-oxylamine)-7-phenoxyquinoline

(SM-10,663; UM 53 g). - To 51 g. (0.2 mole) of 4-chloro-7-phenoxyquinoline⁷³ was added 59.6 g. (0.44 mole) of N-ethyl diethylamine and the mixture was heated and stirred at an internal temperature of 175° for eight hours. At the end of this time the reaction mixture was worked up as previously described using ether and sodium hydroxide solution. The combined

other solutions were washed with three 350 ml. portions of water to remove most of the excess sidechain and after washing were diluted with 200 ml. of benzene and the ether was removed by distillation. The residual benzene solution was dried by removing the benzene-water azeotrope by distillation and was then diluted with 300 ml. of petroleum ether (30-60°) and cooled. An oil separated which crystallized on standing; the solid was removed by filtration and dried. The product weighed 51.3 g. and melted at 98-103°. This material was recrystallized repeatedly from benzene and petroleum ether to a constant melting point of 102-104°. The product so obtained weighed 22.3 g. (30%). Anal. Calc'd. for $C_{24}H_{31}N_3O$: C, 76.55; H, 5.25. Found: C, 76.0, H, 7.9.

7-Chloro-4-(5'-diethylamino-cyclohexylamino)-quinoline. -

A mixture of 12.5 g. (0.062 mole) of 4,7-dichloroquinoline and 21.3 g. (0.124 mole) of 3-diethylamino-cyclohexylamine⁷⁵ was heated and stirred at an internal temperature of 130-140° for 14 hours. The reaction mixture was worked up by the ether extraction method. The ether solution was dried over anhydrous potassium carbonate and concentrated by distillation. The residue was distilled at reduced pressure. A fraction weighing 17.1 g. (53%) and boiling at 215-220° (bath 270-280°) at less than 1 mm. was assumed to be the product.

⁷⁵Supplied by du Pont Experimental Station, Wilmington, Delaware.

3074

7-Chloro-4-(3'-diethylamino-cyclohexyl-amino)-quinoline
diphosphate monohydrate (AN-12,107-S; UM87). - To 12.6 g.
(0.057 mole) of the free base was added 8.75 g. (0.074 mole)
of 85% phosphoric acid. This solution was diluted to turbid-
ity with ethanol and after seeding allowed to stand. An oil
separated which crystallized after standing overnight. The
crystalline material was removed by filtration and dried.
When dry it melted at s-176, m-162-221° and was slightly
yellow in color. After digesting with boiling isopropyl al-
cohol and drying this solid melted at s-219, m-222-230°. This
fraction of salt was combined with small portions from
previous test runs and converted to the free base which was
recrystallized once from benzene and petroleum ether. The
free base was then dissolved in 330 ml. of dioxane; the
theoretical amount of 85% phosphoric acid was added slowly
with stirring and seeding. The resultant mixture was stirred
several hours at 100° and overnight at room temperature. The
salt was then removed and dried (96% recovery from the free
base) to yield material which melted at s-190, m-200-230°. This
solid was digested with boiling isopropyl alcohol to
yield a product which melted 232-230°. Anal. Calc'd. for
 $C_{19}H_{26}ClN_2 \cdot 2H_3PO_4 \cdot H_2O$: C, 41.7; H, 6.27; P, 11.32; H_2O ,
3.50. Found: C, 41.13, 41.65; H, 5.62, 5.84; P, 11.55, 11.57;
 H_2O , 2.96, 3.01.

7-Chloro-4-(4'-diethylamino-1'-cyclohexylamino)-quinoline.

(suspected eutectic). - A mixture of 25.2 g. (0.13 mole) of 4,7-dichloroquinoline and 44.4 g. (0.26 mole) of 4-diethylamino-cyclohexylamine⁷⁵ was heated at 140-150° for four hours and then at 150-165° for three hours. When an attempt was made to work this condensation product up by adding ether and sodium hydroxide solution it was found that the base was not appreciably soluble in the ether. Consequently, after stirring the alkaline slurry well, the solid was removed by filtration and washed with water and dried. When dry the product was dissolved in 150 ml. of ethanol, treated with Norit, and diluted with an equal volume of water. The crystalline material which formed on seeding and cooling was removed and dried after washing with cold 50% ethanol. When dry this material weighed 32 g. (81%) and melted at 147-149°.

⁷⁵This compound was supplied from Lot 5826-112 by the du Pont Experimental Station. This same lot also supplied material for a subsequent run of this compound in which the presence of isomers was first noted. The product from this second run was prepared as reported for this run and a product having the same melting point was obtained. Absorption of these quinoline bases on alumina was being investigated at this time as a method of qualitatively determining the homogeneity of the compounds. The free base from this second run was absorbed on an alumina column from petroleum ether and developed with petroleum ether and benzene. Two distinct zones developed and separation and elution of the alumina with absolute ethanol led to fractions which melted up to 200°. Since only small amounts could be handled in this manner an attempt was made to separate the constituents by fractional crystallization. The first attempts used ethanol as a solvent and failed to give appreciable separation. The use of acetone did yield a material which was richer in the suspected trans form, but by this time a new lot of side-chain had been received which appeared to give a better opportunity of separating the isomers after condensation and no further work was done on this sample.

7-Chloro-4-(4'-diethylamino-1'-cyclohexylamino)-quinoline

Line Diphosphate (suspected eutectic) (SN-12,106-5; UM 26 a.-

To 23.27 g. (0.07 mole) of the free base in 300 ml. of boiling isopropyl alcohol was added slowly with stirring 16.1 g. (0.141 mole) of 85% phosphoric acid. The reaction mixture was seeded, and, after addition of the acid had been completed, it was stirred under reflux for several hours. The reaction mixture was then cooled and the solid removed by filtration, washed with isopropyl alcohol, and dried. When dry it weighed 35 g. (95%) and melted at $m-222.5$, $x-226.3-228^{\circ}$.⁷⁷

7-Chloro-4-(4'-diethylamino-1'-cyclohexylamino)-quinoline

(suspected trans) (SN-14,477; UM 26 a). - To 58.9 g. (0.237 mole) of 4,7-dichloroquinoline was added 100 g. (0.327 mole) of 4-diethylaminocyclohexylamine⁷⁸ and this reaction mixture was heated for five hours at 165-170°. At the end of this time the reaction mixture was dissolved in dilute hydrochloric acid and treated with Dercos. The filtrate was then

⁷⁷ A sample of this material used in a homogeneity determination showed the presence of two components in the ratio of 66:30, which was shown to be a ratio of cis to trans. This finding serves to substantiate the belief that this compound is a eutectic mixture of isomers.

⁷⁸ This sidechain was from Lot 6188-91 supplied by the Gu Pont Experimental Station. In a larger run in these laboratories using sidechain from this lot results were obtained which agree with those reported here.

neutralized with potassium hydroxide solution;⁷⁹ the solid so formed was removed by filtration and dried to yield 71.3 g. (81%) of material which melted at $m-148$, $m-151-150^{\circ}$. This material was dissolved in excess ethanol and separated into fractions by concentration. These fractions were divided by crystallization into further fractions until by combination of similar melting materials there was obtained eventually, after nine recrystallizations from ethanol, 16.2 g. of material which melted at $m-210$, $m-213-222^{\circ}$.⁸⁰ Anal. Calc'd. for $C_{19}H_{25}ClN_3$: C, 69.73; H, 7.90. Found: C, 69.79, 69.86; H, 7.65, 7.33.

7-Chloro-4-(4'-diethylamino-1'-cyclohexylamino)-quinoline (suspected cis). - A mixture of 79.4 g. (0.4 mole) of 4,7-dichloroquinoline and 150 g. (0.82 mole) of 4-diethylamino-cyclohexylamine⁸¹ was heated at $160-170^{\circ}$ for four hours. The reaction mixture was then poured on sufficient sodium hydroxide solution to render the mixture distinctly alkaline and

⁷⁹ The addition of the first small amount of alkali resulted in the precipitation of a small amount of an orange solid. This material was removed by filtration before the neutralization was continued. It was not identified.

⁸⁰ The homogeneity was not determined on this sample itself. However, a homogeneity determination made on another fraction of product prepared by condensation of sidechain from the same lot showed a homogeneity of 92%.

⁸¹ Supplied by du Pont Experimental Station where it had been prepared by reduction over a catalyst not designated.

V S O N J O W H

V S J O W H O J W O J W O J W O

the sidechain was removed by steam distillation. The solid residue was washed with water and dried to yield a solid which melted at 110-140°; from this solid by a series of six recrystallizations from ethanol it was possible to obtain 19.6 g. of material melting s-155, m-156.6-158.6° which was suspected to be the sis isomer.⁶² Anal. Calc'd. for C₁₉H₂₆ClN₂: C, 68.75; H, 7.90. Found: C, 68.24, 68.29; H, 7.70, 7.74.

N-(2-Chloroethyl)-phthalimide.⁶³ - To 124 g. (0.87 mole) of potassium phthalimide suspended in one liter of acetone was added 143 g. (1.0 mole) of ethylene dichlorobromide. The resultant mixture was stirred at reflux temperature of the acetone for 18 hours. The solid was removed by filtration, the filtrate concentrated, and the residue distilled at reduced pressure. The fraction boiling at 132-134° (bath 190-199°) at about 100 microns was assumed to be product. It was poured while still molten into 150 ml. of ethanol and allowed to crystallize. The solid removed by filtration and dried weighed 119 g. (92%) and melted at 76-79°. It was considered

⁶²This material was shown to be 93% homogeneous.

⁶³This compound has been described previously by Wanker, J. Am. Chem. Soc., 59, 482 (1937), who prepared it from N-(2-hydroxyethyl)-phthalimide and phosphorus pentachloride in crude yield of 94%. Clemo and Matton, J. Chem. Soc., 735 (1928), report its preparation in a crude yield of 86% by reaction of potassium phthalimide and 2-chloroethyl-p-toluene sulfonate. It was also prepared from ethylene chloride and potassium phthalimide heated in a sealed tube at 180-190° by Salts, Ber. 34, 2526 (1891). All investigators reported, after repeated recrystallization, a melting point of 79-81°.

to be sufficiently pure for the next step.⁵⁴

8-Methoxy-8-(2'-phthalimidoethyl)-guineline.⁵⁵ - The

temperature of a mixture of 215 g. (1.1 moles) of N-(2-chloroethyl)-phthalimide and 368 g. (8.2 mole) of 8-amino-6-methoxyguinoline was raised slowly over a four hour period to an internal temperature of 125°. The temperature was then gradually raised to 135° over an 18 hour period. At the end of this time dilution of the reaction mixture with 400 ml. of methanol resulted in the crystallization of a light yellow solid which when removed by filtration, washed with methanol and ether, and dried weighed 246 g. (58%). This solid was suspended in chloroform and shaken with an excess of aqueous potassium carbonate. The chloroform solution when dried and concentrated deposited 185 g. (45%) of product which melted at 149-150°. This material was adjudged sufficiently pure for the next step.

⁵⁴This compound was also prepared by the reaction of phthalic anhydride with ethanol amine and the subsequent reaction of the hydroxyethyl phthalimide with thionyl chloride. These reactions gave an 83% overall yield of a product which resisted all efforts to raise its melting point above 73-75°. A portion of the intermediate N-(2-hydroxyethyl)-phthalimide which was isolated before reaction with the thionyl chloride had the correct melting point.

⁵⁵This compound had been prepared previously by Baldwin, J. Chem. Soc., 2959 (1929), using bromoethylphthalimide; he reported difficulty in isolating the product. Quin and Robinson, J. Chem. Soc., 535 (1943), who used Baldwin's directions report preparing the compound in 42% yield and report its melting point as 152°.

8-(2'-aminoethylamino)-6-methoxyquinoline Dihydro-
chloride.⁸⁶ To 175 g. (0.505 mole) of 8-(2'-phthalimi-
doethylamino)-6-methoxyquinoline was added 1000 ml. of
ethanol and 33.6 g. (0.555 mole) of 85% hydrazine hydrate.
This mixture was heated under reflux for two and one-half
hours with stirring and was then cooled to room temperature.
The solid present was removed by filtration and the filtrate
was concentrated to dryness by distillation under reduced
pressure. The solid removed by filtration was returned to
the flask, 1000 ml. of water and 190 g. (1.23 mole) of con-
centrated hydrochloric acid were added, and the semi-solid
mass which resulted was heated at 100° for one-half hour.
At the end of this time the precipitated phthalylhydrazide
was removed by filtration, and the aqueous filtrate was con-
centrated under reduced pressure to ca. 700 ml. To this
aqueous solution acetone was added to incipient turbidity,
and upon cooling there was obtained 112 g. (77%) of the
product which melted at m-260, n-263-265°. The filtrate from
the precipitation of the salt was concentrated and rendered
strongly basic with aqueous sodium hydroxide. The base was
extracted with ether and the resultant solution was concen-
trated by distillation of the ether. The residue was distilled

⁸⁶ Prepared also by Baldwin and by Quin and Robinson (see
65). They report melting points of 263-264° and 248° respec-
tively.

from a Hickman type molecular still to yield 15.26 g. (14%) of product which distilled rapidly at a pressure of 12 microns and with a bath temperature of 170°.

The monohydrochloride of this compound was prepared and recrystallized from 85% aqueous sodium chloride and finally from absolute ethanol and ether to a constant melting point of 2-206, m-207-212° with decomposition. Anal. Calc'd. for $C_{12}H_{15}N_2O \cdot HCl$: Cl, 12.98. Found: Cl, 14.06, 14.08.

N-(3-Chloropropyl)-phthalimide.⁸⁷ - This compound was prepared from trimethylene chlorobromide and potassium phthalimide in the manner used for the preparation of the corresponding ethyl compound previously described. Instead of distilling the product, however, the residue after the removal of solvent and excess chlorobromide was poured into its own volume of ethanol and allowed to crystallize. One further crystallization yielded a product which melted at 64-69° and was adjudged sufficiently pure to use in the coupling reaction inasmuch as the most probable impurity would be the corresponding bromo compound which would also couple with the nucleus to yield the desired compound.

⁸⁷ This compound was prepared previously by Gabriel, Ber., 38, 2526 (1905), by Megidson and Grigorevskii, Rus., 62, 596 (1936), and by Beletsvetov and Ismail'skii, J. Gen. Chem. (U. S. S. R.), 14, 216 (1944), who record melting points from 62-68.5

5-Methoxy-8-(5'-phthalimidopropylamino)-quinoline.⁸⁸ -

The preparation of this compound has been described fully by Mosher and Klesinger, Von, and Carmack and for that reason is not completely described here. The compound having a melting point of 101-103° was prepared in 44% yield. There was also obtained a 36% yield (based upon bromopropylphthalimide) of what on the basis of Mosher's work was assumed to be 8-(bis-(3-phthalimidopropyl)-amino)-5-methoxyquinoline.

8-(5'-aminopropylamino)-5-methoxyquinoline dihydrochloride.⁸⁹ - This compound was prepared exactly as described for the corresponding ethyl compound; a yield of 88% was obtained.

N-(4'-Bromobutyl)-phthalimide.⁹⁰ - To 150 g. (0.6 mole)

⁸⁸ Prepared previously by Baldwin, *J. Chem. Soc.*, 2659 (1924), by Baldwin and Robinson, *J. Chem. Soc.*, 1264 (1934), by Glen and Robinson, *J. Chem. Soc.*, 557 (1943), by Nagieson and Bobychev, *J. Gen. Chem. (U. S. S. R.)*, 2, 593 (1933), by Klesinger, Von, and Carmack, *J. Am. Chem. Soc.*, 68, 1563 (1946), and by Mosher, *J. Am. Chem. Soc.*, 68, 1565 (1946). All of these sources report melting points in the range of 101-103° and report yields ranging from 36-55%. Mosher, who paid particular attention to the by-products of the reaction, reported also a 2.7% yield of the 8-(bis-(3-phthalimidopropylamino)-5-methoxyquinoline.

⁸⁹ This compound has previously been prepared. (See references in 85).

⁹⁰ Robinson and Sugimasek, *J. Chem. Soc.*, 299 (1932), report the preparation of this compound in 50% yield with a melting point of 56.5-57° from the reaction between N-(4'-hydroxybutyl)-phthalimide and hydrobromic acid. Cope, (private communication to Dr. H. L. Drake), reports its preparation in 45% yield and with a melting point of 78-79° by heating tetramethylene bromide with potassium phthalimide at 180-185° for 10 hours.

of tetramethylene bromide in 500 ml. of acetone at reflux temperature was added in four portions over a period of four hours 37 g. (0.2 mole) of potassium phthalimide. The reaction mixture was stirred and refluxed for a total of 18 hours after which time it was cooled to room temperature, and the potassium bromide was removed by filtration and washed with fresh acetone. The filtrate and washings were combined and concentrated by distillation of the acetone. The residue was distilled under reduced pressure to yield 39 g. of material boiling 159-161° (bath 210°) at about 300 microns. This material after one recrystallization from ethanol weighed 36 g. (64%)⁹¹ and melted at 75-76°.

6-Methoxy-8(4'-phthalimidebutylamino)-quinoline and
8-(4'-Aminoethyl amino)-6-methoxyquinoline Dihydrochloride.⁹² -

5-Chloro-1-pentanol. - To 515 g. (4.93 mole) of pentamethylene glycol was added 1200 ml. (14.9 mole) of concentrated hydrochloric acid. This solution was heated at an internal

⁹¹This does not represent the optimum yield for this reaction. On subsequent runs the yield has been increased 10-20% while producing material of comparable or superior quality. The reaction has also been applied with similar yields to the preparation of the corresponding amyl and ethyl compounds.

⁹²These compounds were prepared elsewhere in these laboratories but by methods similar to those described for the corresponding ethyl and propyl compounds. It was noted in the coupling of the bromoalkylphthalimides that considerable care was necessary to prevent the reaction, which is very exothermic, from becoming too violent.

temperature of 65-80° and continuously extracted with toluene. The extraction and heating were continued over a forty hour period using three 1500 ml. portions of toluene. After about 28 hours the aqueous layer was saturated with hydrogen chloride by the introduction of the anhydrous gas. The three toluene extracts were combined and concentrated. The residue, distilled through a two foot Vigreux column, yielded 320 g. (53%) of product boiling 107-109° (bath 155°) at 24 mm. It had a refractive index of 1.4497²⁵. This compound formed an alpha-naphthyl urethane which melted at 71.6-72.6°.²⁵

8-(3'-Hydroxyamylamino)-6-methoxyquinoline. - To 174 g. (1.0 mole) of 8-amino-6-methoxyquinoline was added 61 g. (0.5 mole) of 5-chloro-1-pentanol and the resultant mixture was stirred at 125° for four and one-half hours. At the end of this time the precipitated solid made stirring almost impossible; to facilitate stirring and to prevent overheating, 65 ml. of water was added and an internal temperature of 87° was maintained for 13 hours. The internal temperature was then raised to 105° for four hours. The reaction mixture was cooled and made strongly alkaline by the addition of aqueous sodium hydroxide. The two phase system was extracted exhaustively with ether, and the ether extract was then dried

²⁵

Bennett and Heathcoat, J. Chem. Soc. 265 (1929), give 72°.

and concentrated. The residue was distilled under reduced pressure to yield a 106 g. portion of unreacted nucleus boiling at 110-115° (bath 140-155°) at about one micron and a 70 g. fraction boiling at 175-180° (bath 200-230°) at less than one micron which was assumed to be the product. This represents a yield of 69% based upon unrecovered nucleus. A portion of this material upon standing crystallized to form a solid which melted indefinitely below 60°. A picrate prepared from this material melted at 138-139° after crystallization from acetone and water.⁹⁴

1-Bromo-3-chloropentane.⁹⁵ - To 105 g. (0.84 mole) of pentamethylene chlorohydrin in 200 ml. of absolute ether was added slowly 229 g. (0.84 mole) of phosphorus tribromide dissolved in 100 ml. of absolute ether. After the addition was completed the mixture was heated under reflux for two hours. The ether solution was washed with water and then with dilute sodium hydroxide solution⁹⁶ and finally was dried over

⁹⁴Lee, Synthesis of Chemotherapeutic Agents (Thesis, Magdalen College, Oxford, 1946), gives a melting point of 142-146°.

⁹⁵Prepared by Magidson and Grigorovskii, Ber., 69, 396 (1936), from N-(5-chloroacetyl)-benzamide by reaction with phosphorus tribromide and then with bromine. They give a boiling point of 210-212° and refractive index of n_D^{20} -1.4920.

⁹⁶In view of the ease with which the pentamethylene halohydrins cyclize to form tetrahydropyran this step is probably responsible for the low yield in this reaction. Washing with water alone should suffice to remove the phosphoric acid resulting in the reaction.

anhydrous magnesium sulfate and concentrated. The residue was distilled at reduced pressure to yield a 105.5 g. (67%) fraction boiling at 89-90° (bath 125-135°) at 20 mm. This material had a boiling point of 198° at 763 mm, and refractive indices of n_D^{18} -1.4829 and n_D^{25} -1.4797.

N-(3-Chlorocarbonyl)-phthalimide,⁹⁷ - To 100 g. (0.54 mole) of 1-bromo-3-chloropentane in 1000 ml. of acetone was added 100 g. (0.54 mole) of potassium phthalimide and the resultant mixture was stirred and heated under reflux for 48 hours. At the end of this time it was cooled to room temperature and the solid was removed by filtration and washed with fresh acetone. The filtrate and washings were combined and concentrated. The residue was distilled at reduced pressure to yield 92 g. (66%) of product boiling 159-161° (bath 210-220°) at ca. 300 microns. The product had a refractive index of n_D^{25} -1.5533.

6-Methoxy-3-(3'-phthalimidocarbonylamino)-quinoline,⁹⁸ - To 92 g. (0.366 mole) of N-(3-chlorocarbonyl)-phthalimide was added 126 g. (0.732 mole) of 6-amino-6-methoxyquinoline, and this reaction mixture was stirred and heated at 150° for 20 hours. At the end of this time it was diluted with 400 ml. of

⁹⁷ This compound had previously been prepared by Gabriel, *Ber.*, **42**, 4080 (1909), from 1,3-diphthalimidopentane. It was reported to be crystalline melting at 80-81°.

⁹⁸ Baldwin, (see 65), prepared this compound, m.p. 117-118°, in 50% yield using the bromophthalimide.

methanol and then with 1600 ml. of ether. The solid which separated weighed 159 g. when dry. A 119 g. portion of this material was thoroughly mixed with aqueous sodium carbonate in a Waring Blender. The resultant larry material was washed with several portions of water in the same manner. Upon the addition of 270 ml. of methanol and further stirring, this material became crystalline and was removed by filtration. This material when dried weighed 88.5 g. (59%, assuming the entire 159 g. would have been converted in the same yield) and melted at 114-117.5°. A portion of this material, recrystallized from acetone in good yield, melted at 8-116, m-117-118°. Anal. Calc'd. for $C_{22}H_{22}N_2O_3$: C, 70.19; H, 5.95. Found: C, 70.95, 70.96; H, 6.01, 5.90.

8-(5'-Aminoacetylamino)-6-methoxyquinoline Dihydrochloride. 99

- To 70.6 g. (0.181 mole) of 6-methoxy-8-(5'-phthalimidocetylamino)-quinoline in 380 ml. of ethanol was added 11.9 g. (0.301 mole) of 85% hydrazine hydrate. The mixture was heated under reflux for four hours. The alcohol was removed by distillation at reduced pressure¹⁰⁰ and the residue was treated with 350 ml. of water and sufficient concentrated

⁹⁹Prepared previously by Baldwin, J. Chem. Soc., 2959 (1929), who reported obtaining the dihydrochloride trihydrate upon recrystallisation from 95% ethanol.

¹⁰⁰This operation is considerably facilitated by removing the solid present at the beginning of the distillation by filtration and returning it to the flask after concentration of the filtrate.

hydrochloric acid to render the mixture acid to Congo Red paper. The resultant mixture was heated at 100° for 40 minutes, cooled, and filtered with suction. The solid was washed with fresh water, and the washings and filtrate were combined and concentrated by distillation under reduced pressure to a volume of about 300 ml. This residue was diluted to turbidity with acetone and set aside. The solid which resulted was removed by filtration and washed with acetone. When dried it weighed 61.5 g. (88%, assuming trihydrate) and melted at m-83, m-84-104°.¹⁰¹

N¹-(2-(6-methoxy-8-quinolylamino)-ethyl)-guanidine

Bilirubin (64.168 g). - To 18.88 g. (0.07 mole) of 6-(8'-aminoethylamino)-8-methoxyquinoline dissolved in 50 ml. of propanol and 10 ml. of water was added 10.45 g. (0.075 mole) of 3-methyl-isothiouracil sulfate and the resulting mixture was heated at reflux temperature of the mixed solvent for 18 hours. At the end of this time the solution was concentrated slightly and diluted with acetone to cause the precipitation of a plastic mass. This material was washed with several portions of acetone and finally with one of ethanol whereupon it crystallized. The ethanol was diluted with acetone and

¹⁰¹ depending upon the treatment accorded it during re-crystallization this material could be caused to melt in any of three ranges, i.e. 83-86°, 104-107°, and 220-225°. Each melting point was marked by very apparent decomposition of the material. It is suggested that these are melting points of the trihydrate, the monohydrate, and the anhydrous product. The material as obtained from the reaction was found to be satisfactory for all further investigations.

the resultant solid removed by filtration and dried to yield 19 g. of crude product sulfate. A 17 g. portion of this material was suspended in water and treated with a large excess of concentrated sodium hydroxide solution. The guanidine free base was then extracted with one 60 ml. portion of butanol. The butanol solution was washed with several small portions of water and finally filtered and diluted to ca. 600 ml. with ether. Small pieces of dry ice were added to the ethereal solution until no farther solid was precipitated. This solid was removed by filtration and washed with ether and quickly dried. There was obtained 10 g. of the guanidine carbonate.¹⁰² A 1 g. portion of this solid was dissolved in ca. 50 ml. of ethanol and titrated with alcoholic hydrogen chloride.¹⁰³

On the basis of the titration of the aliquot the amount of acid required to prepare the dibasic salt of the total solid could easily be determined. After addition of the required amount of acid, the solution was warmed and diluted to turbidity with acetone. Upon cooling there was obtained 10 g. of dihydrochloride. The dihydrochloride was dissolved in 15 ml. of water and heated to boiling; there was then added 20 ml. of 50% aqueous ammonium nitrate. Upon cooling

¹⁰² Attempts to recrystallize and so purify these carbonates were unsuccessful.

¹⁰³ The first equivalent of the alcoholic acid could be added with almost no change in the color of the solution. There is, however, a sharp color change as the first small amounts of dibasic salt are formed.

the crystalline nitrate was obtained and was removed by filtration. It was again dissolved in water, and the treatment with ammonium nitrate was repeated. A portion of this solid when dissolved in water and acidified with nitric acid did not give a test for chloride ion upon the addition of aqueous silver nitrate. The solid was dissolved in 25 ml. of water and diluted with 500 ml. of absolute ethanol. This solution was then concentrated to ca. 200 ml. and cooled and the solid formed was removed by filtration. This recrystallization was repeated three times to yield 7 g. (29%)¹⁰⁴ of product which melted at $s-161$, $m-195-198.5^{\circ}$. Anal. Calc'd for $C_{15}H_{17}N_3O^+$ $2HNO_3$: C, 40.31; H, 4.96. Found: C, 40.34, 40.55; H, 5.16, 5.45.

N^1 -(3-(6-methoxy-8-quinolyamino)-propyl)-guanidine

Dinitrate (UN 161 4). - This compound was prepared exactly as described for the corresponding ethyl compound.¹⁰⁵ Considerable portions of this compound were used in the early attempts to find a method of purifying these guanidines, but

¹⁰⁴Except for the purification of the guanidine through the carbonate other intermediate steps above are not believed to be essential. Titration of the carbonate with dilute nitric acid would probably serve to increase the yield considerably. The steps as reported were adopted because they seemed at the time to be expedient. It was originally intended to purify the hydrochlorides but they were found to be so hygroscopic as to render them very difficult to work with. Some other non-hygroscopic salt consequently was sought; the nitrate seemed best to fit the requirements.

¹⁰⁵During the course of the preparation of this compound a portion of the dihydrochloride was purified to a constant melting point of $s-253$, $m-234-255.4^{\circ}$.

after these experiments had been completed there remained an 18% yield of the purified compound. When recrystallized to constant melting point the product melted at s-219, m-221.5-228°. Anal. Calc'd for $C_{14}H_{19}N_3O \cdot 2 HNO_3$: C, 42.10; H, 5.50. Found: C, 42.07, 42.37; H, 5.40, 5.42.

N^1 -(4-(6-methoxy-8-quinolylamino)-butyl)-guanidine Dinitrate (UM 143). - This compound was prepared exactly as described for the corresponding ethyl compound. There was obtained a 55% yield of material which melted at s-173, m-173.5-174.5°. Anal. Calc'd. $C_{18}H_{21}N_3O \cdot 2 HNO_3$: C, 43.37; H, 5.60. Found: C, 43.44, 43.57; H, 5.56, 5.60.

N^1 -(5-(6-methoxy-8-quinolylamino)-amyl)-guanidine Dinitrate (UM 142). - This compound was prepared in the manner described for the ethyl compound.¹⁰⁶ There was obtained a 25% yield of product recrystallized to a constant melting point of s-180, m-182-185°. Anal. Calc'd. for $C_{18}H_{25}N_3O \cdot 2 HNO_3$: C, 44.96, H, 6.90. Found: C, 44.97, 45.16; H, 6.06, 6.00.

Sakaguchi Test Method.¹⁰⁷ To 5-10 mg. of the substituted

¹⁰⁶ During the course of the preparation of this compound the dihydrochloride was recrystallized to constant melting point of s-215, m-214-216°.

¹⁰⁷ Sakaguchi, J. Biochem. (Japan), 5, 153 (1925); C. A., 20, 925 (1926). See also Koch, Practical Methods in Biochemistry (Baltimore, Maryland: Williams and Wilkins, 1941).

guanidine dissolved in 4 ml. of water was added 3 ml. of 15% aqueous sodium hydroxide and 4 ml. of 0.013% solution of naphthol-1 in water. This mixture was thoroughly shaken. If a precipitate developed at this point it was removed by filtration. To the clear solution was added several drops of a solution of sodium hypobromite prepared by saturating a 0.5% solution of sodium hydroxide with bromine. The immediate formation of a bright red color upon the addition of the hypobromite indicated the presence of a monoalkyl-guanidine.

Isopropylisothiocyanate.¹⁰⁸ - To 330 g. (4.6 mole) of carbon disulfide was added 500 ml. of water and 322 g. (3.8 mole) of sodium hydroxide and this mixture was cooled and stirred at ice-bath temperature while 256.4 g. (4.0 mole) of isopropyl amine was added slowly. The resultant slurry was stirred while being cooled in the ice-bath for one hour. It was then allowed to warm to room temperature and was stirred occasionally over a period of one and one half hours. The solid was removed by filtration and was then suspended in 1000 ml. of water and treated, while being stirred, with 1532 g. (4.0 mole) of lead nitrate dissolved in 2200 ml. of water. The resultant mixture was steam distilled until a one phase distillate was obtained. The organic layer was

¹⁰⁸ Prepared by Jahn, Monatsh., 3, 163 (1862), who reported a boiling point of 137-137.5°.

removed from the aqueous distillate, washed with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. It was then distilled to yield 330 g. (62%) of isopropylisothiocyanate boiling 156-158° (bath 165-165°).

Isopropylthiourea.¹⁰⁹ - To 600 ml. (9.0 mole) of concentrated ammonium hydroxide was added slowly with vigorous stirring 150 g. (1.49 mole) of isopropylisothiocyanate. After addition was complete the reaction mixture was stirred for 10 hours. It was then cooled in an ice-bath and the solid was removed by filtration. When dried it weighed 171 g. (97%) and melted at 167-169°.

N-Isopropyl-S-methyl-isothiourea Picrate. - To 25.6 g. (0.2 mole) of isopropylthiourea in 80 ml. of absolute ethanol was added 48.6 g. (0.3 mole) of methyl iodide. The mixture was heated slightly while the methyl iodide refluxed gently for three hours. The solvent was removed by distillation at reduced pressure. The residual syrup when treated with an excess of alcoholic picric acid immediately precipitated the yellow crystalline picrate. Recrystallization to constant melting point of α -165, α -166-167° from ethanol yielded 41.2 g. (37%) of the product. Anal. Calc'd. for $C_{11}H_{15}N_2O_7$: C, 36.86; H, 4.17. Found: C, 36.79, 36.75; H, 4.43, 4.39.

¹⁰⁹ Prepared previously by Jahn, (see 108), who reported a melting point of 167°, and by May, J. Org. Chem., 12, 437 (1947), who reported a melting point of 167-167.5°.

ABSTRACT

John A. Garman, Ph. D., 1948, (B. S. Franklin and Marshall College)

Title of thesis: Synthetic Antimalarials

Thesis directed by Dr. Nathan L. Drake

Major: Organic Chemistry

Minors: Physical and Inorganic Chemistry

Pages in thesis, 58. Words in abstract, 180.

This paper describes the preparation and properties of fifteen potential antimalarial drugs each of which belongs to one of the following classes: (1) substituted sulfonamides, (2) substituted aminoalcohols, (3) 6-aminoquinolines, and (4) 8-aminoquinolines. The preparation of a number of intermediate compounds which are also new is described as are the syntheses of a series of known compounds which have been prepared by new, different, or improved methods.

The preparation of the following potential antimalarial drugs has been described: 5'-chloro-6'-dimethylamino-sulfanilamide, 8¹-(5-bromo-1-naphthyl)-sulfanilamide, 8¹-(5-quinolyl)-sulfanilamide, α -(6'-bromo-4-biphenyl)- β -dibutylaminoethanol hydrochloride, α -(4'-bromo-4-biphenyl)- β -diethylaminoethanol hydrobromide, 4-(1'-diethylamino-4'-aniline)-6-methoxy-8-phenylquinoline triphosphate, 4-(1'-diethylamino-4'-aniline)-8-phenoxyquinoline, 7-chloro-4-(1'-diethylamino-6'-hexylamino)-quinoline diphosphate, 4-(1'-diethylamino-4'-aniline)-7-phenoxyquinoline, 7-chloro-4-(5'-diethylaminocyclohexylamino)-quinoline diphosphate monohydrate, 7-chloro-4-(4'-diethylaminocyclohexylamino)-

quinoline (suspected cis, trans, and eutectic forms), N¹-
(2-(6-methoxy-8-quinolylamino)-ethyl)-guanidine dinitrate,
N¹-(2-(6-methoxy-8-quinolylamino)-propyl)-guanidine dini-
trate, N¹-(4-(6-methoxy-8-quinolylamino)-butyl)-guanidine
dinitrate, and N¹-(6-(6-methoxy-8-quinolylamino)-amyl)-
guanidine dinitrate. All of these compounds with the ex-
ception of the N¹-(8-quinolyl)-sulfanilamide are new com-
pounds.

Incidental to the preparation of the above compounds a
number of new intermediates have been described, namely:
N-acetylsulfanilamide-3-chloro-4-dimethylaminobenzene, 1-
acetylauranilamide-5-bromonaphthalene, 4-(4'-bromophenyl)-
phenacyl bromide, ω-di-n-butylamino-4-(4'-bromophenyl)-
acetophenone hydrochloride, ω-diethylamino-4-(4'-bromophenyl)-
acetophenone hydrochloride, 4-(1'-diethylamino-4'-oxylamino)-
6-methoxy-3-phenylquinoline, 7-chloro-4-(1'-diethylamino-6'-
hexylamino)-quinoline, 7-chloro-4-(5'-diethylaminocyclohexy-
lamino)-quinoline, 8-(5'-hydroxyamylamino)-6-methoxyquinoline
and its picrate, N-isopropyl-5-methyl-isothiourea picrate.

A discussion of attempted preparations of some quino-
line substituted biguanides and some dialkylguanidines is
also included.

VITA

Name: John Andrew Garman

Permanent Address: 530 Main Street, Berlin, Pennsylvania

Degree to be conferred; date: Ph. D.; June 3, 1948

Date of birth: August 3, 1921

Place of birth: Berlin, Pa.

Secondary Education: Berlin-Brothersvalley High School,
Berlin, Pa.

| Collegiate Institution Attended | Dates | Degree | Date of Degree |
|---------------------------------|-----------|--------|----------------|
| Franklin and Marshall College | 1939-1943 | B. S. | February, 1943 |

Publications: J. Am. Chem. Soc., 68, 1298 (1946); Ibid., 68,
1214 (1946); Ibid., 68, 1829 (1946); Ibid., 68 163A (1946);
J. Org. Chem., II, 795 (1946).

Present position: Research Fellow, University of Maryland,
College Park, Md.

Prospective position: Research Chemist, Firestone Tire and
Rubber Co., Pottstown, Pa.