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THE SYNTHESIS OF $N^1$-(6-METHOXY-8-
QUINOLYLAMINOALKYL)–$N^5$-ISOPROPYL
DIGUANIDES AND INTERMEDIATES.

By
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INTRODUCTION

Probably no field of chemotherapy has received more attention than that pertaining to the treatment of malaria. There has been an unprecedented and coordinated effort along this line during the past ten years. Although much progress has been made in exploring over 14,000 chemical compounds\(^1\) no completely satisfactory drug was disclosed. Any attempt, therefore, to provide a logical exposition of potential antimalarial compounds is assuming too much liberty. Unfortunately there is no known means of pre-determining which compound will be a cure. The compounds chosen for study in the past were selected either because of alleged antimalarial activity, because of known chemotherapeutic effect in other diseases, or because they were chemical analogues of drugs with known antimalarial effect in man or animals. The latter reason is the basis for the work presented in this thesis.

Chemotherapeutic agents in general use in malaria exhibit a highly selective action. Drugs capable of eradicating trophozoites of the erythrocytic cycle are incapable of a like action on preerythrocytic forms.\(^2\) Conversely, drugs potent against preerythrocytic parasites are largely without effect on erythrocytic forms.\(^3\) Quinine, atebrin and chloroquine, as far as practical


\(^3\) \textit{Ibid.}
benefit against asexual forms is concerned, are active only on erythrocytic forms.\textsuperscript{1} Plasmochin acts exclusively on exoerythrocytic forms.\textsuperscript{4} The newer approach demands that therapy be directed toward the prevention of the exoerythrocytic type of relapse as well as toward the erythrocytic type. Either a single drug must be discovered which has the dual capacity of acting against the parasites of both exoerythrocytic and erythrocytic phases, or a combination of two drugs which will accomplish the same result must be used. The ideal malaria drug must act as a prophylactic, cure both acute and latent infections, have only minor toxic qualities, and be effective against all species of the human parasite.

\textsuperscript{1}N-(p-Chlorophenyl)-N'-isopropyl diguanide, paludrine, I, appears unique, since it represents the first discovery of a drug which has appreciable dual activity against both erythrocytic and exoerythrocytic forms.\textsuperscript{5}

\begin{equation*}
\text{I}
\end{equation*}

\textsuperscript{4}Roehl, Naturwissenschaften, 14, 1156 (1926).

Some success has been achieved by the simultaneous use of combining quinine with either one of the following two drugs: 8-(5-isopropylaminoamylamino)-6-methoxyquinoline (pentaquine), II, and 8-(4-isopropylamino-1-methylbutylamino)-6-methoxyquinoline (isopentaquine), III.

Both show a high percentage of cures without too serious accompanying toxic reactions. In combination with quinine they provide an attack on forms of both cycles.

Paludrine has not been found to exert greater effect on the relapse rate of vivax malaria after treatment of a clinical attack than has atebrin. In this respect it falls short of the criteria for the ideal antimalarial drug. However, its suppressive activity in low dosage, its wide range between effective and toxic dosage, and its cheapness of manufacturing costs make it compare favorably with all other antimalarial drugs. It is highly probable that paludrine is not the ultimate drug of choice in the diguanide series, and the ease with which this group of compounds can be manipulated offers many possibilities for further study.

\[6\text{Loeb, J. Am. Med. Assoc., 132, 321 (1946).}\]
It is interesting to follow the line of reasoning that first prompted Curd and Rose to test the antimalarial activity of molecules containing the diguanide group. 7

In their development of new antimalarial drugs containing the pyrimidine ring system activity was first encountered in the p-chloranilino type represented by the compound 2666, IV.

Schonhofer had attempted to correlate antimalarial activity in the synthetic quinoline series with the tautomeric possibilities of the molecule. 8 It was evident that in compound 2666 and later in other related active compounds a number of tautomeric forms was possible. The postulate was then advanced that the possibility of tautomerism and of conjugation occurring through a chain of alternate carbon and nitrogen atoms may be a determining feature for antimalarial activity in this type of molecule. This conjugation may be further extended to include the aryl nucleus so that substituents in the benzene ring play a significant part. On the basis of this working hypothesis, attention was directed toward placing a guanidino group between the aryl group and the pyrimidine nucleus and the even more active compound 3349, V, was synthesized.

\[ \text{IV} \]

\[ \text{V} \]

A stepwise simplification of structures IV and V was then attempted with the idea of simplifying the drug molecule and clearing it of unnecessary detail, leaving only those groupings which were essential for antimalarial activity. Both structures were strong bases, and it was tentatively assumed that this property had to be retained in subsequent compounds. The 4-methyl group in the pyrimidine ring was not originally thought to have any special significance, having been introduced incidentally as the result of the method of synthesis, and it was proposed that it should be omitted. Further, if the function of the pyrimidine ring was merely to act as a convenient frame in which to arrange the conjugated carbon and nitrogen atoms, then the entire unit (positions 4 and 5) of the pyrimidine nucleus might also be considered inessential, and it was suggested that while a pyrimidine ring provided a convenient means for the synthesis of structures containing the salient features, that any heteroenoid system of that type might be expected to function in the same manner and the cyclic system could be dispensed with in this portion of the drug molecule. There then remained in case of structures IV and V respectively the following skeletal configurations which were thought necessary for activity:

$$\text{VI}$$

$$\text{VII}$$

VI appeared as a derivative of diguanide and VII as a derivative of an extended diguanide. From this point on further variation of molecular detail of $R$ group in structure VI to that of the
isopropyl group culminated in paludrine, I, the compound with the highest activity in its class.

Considerable modification of the basic diguanide structure VIII was made immediately after the discovery of paludrine activity, with the idea of synthesizing an even more desirable antimalarial drug.

\[ \text{N} \equiv \text{H} \quad \text{N} \equiv \text{H} \]
\[ \text{N} - \text{C} - \text{N} - \text{O} - \text{N}^\text{R} \]

The replacement of the isopropyl group at \( N^5 \) in paludrine by a hydrogen atom, another alkyl group,\(^7\) a dialkyl group,\(^9\) or an aryl group,\(^10\) greatly reduced the antimalarial effect as did the introduction of a methyl or an ethyl group at \( N^1 \) in place of the hydrogen atom.\(^11\) Fuller studying the antibacterial action of aryl diguanides noted that when \( N^1 \) is alkylated, there is no pronounced change in bacteriostatic properties but if the terminal \( N^5 \) is alkylated there is a distinct enhancement of bacteriostatic properties.\(^12\) Gage looked in vain for a difference in ultraviolet absorption spectra to explain the difference in antimalarial activity of various alkyl groups in the \( N^5 \) position.\(^13\)

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\(^9\)Bami, Natarajan, Ramaswamy, et al., Current Science (India), 142, 50-2 (1949).
cyano and thio groups replacing the $R$ in figure VIII, and the
dioxymethylene, methyl, ethyl, acetyl, methoxy and ethoxy groups
in the ortho, para, and meta positions did not displace the chlorine
in the paludrine nucleus as the most effective of the variants ex-
amined. An assay of $N^1$-p-bromophenyl-$N^5$-isopropyl diguanide has
disclosed that it possesses somewhat higher antimalarial activity
than paludrine. $N^1$-3,4-Dichlorophenyl-$N^5$-isopropyl diguanide is
more active than paludrine but much more toxic.

A series of homologous $N^2$, $N^5$ alkyl and $N^4$, $N^5$ alkyl derivatives
were prepared and when alkyl groups were attached to either $N^2$ or $N^4$
on the originally highly active paludrine a dystherapeutic effect on
antimalarial activity resulted. Similar results were found
with $N^2$, $N^4$, $N^5$ derivatives.

Deamination of paludrine at $N^2$ to give the $N$-p-chlorophenyl-
$N^1$-isopropylguanyl urea decreased the molecule's antimalarial action
profoundly. Benzimidazoles formed by loss of a hydrogen atom from
$N^2$ and the ortho position in the benzene ring of paludrine are entirely
without action on malaria parasites.

Ainley, Curd and Rose, ibid., 98 (1949).
Birtwell, Curd, Hendry and Rose, ibid., 1645 (1948).
Ashworth, Crowther, Curd, Hendry, Richardson and Rose, ibid.,
475 (1949).
Curd, Davey and Richardson, ibid., 1732 (1949).
Considerable variation in the position has been reported wherein the p-chlorophenyl group in paludrine is replaced with other aryl nuclei. The xylyl, phenacyl, diphenyl, 6-bromo-2-naphthyl, benzyl, cinnamyl, p-chlorobenzyl, p-chlorophenylsulfonyl, and phenanthryl and 3-chloro-6-phenanthryl groups have been tested without displaying notable activity.

Of real theoretical interest is the combination of the highly active quinoline nucleus and the diguanide side chain. Spinks has shown that paludrine exhibits absorption and distribution characteristics qualitatively similar to those of atebrin and quinine. On the assumption that the basic side chain of the older antimalarial compounds is primarily responsible for these properties, he suggested that the isopropyl diguanide residue of paludrine, besides being concerned with the intrinsic antimalarial activity, also simulated the alkylaminoalkylamino group (figures II and III) in its effect on absorption. Accordingly in place of the para-chlorophenyl group in paludrine the 8-quinolyl, 6-quinolyl, 8-chloro-6-quinolyl, 8-chloro-5-quinolyl, 4-hydroxy-5-quinolyl, and 6-methoxy-3-quinolyl diguanides have been synthesized. The 8-chloro-5-quinolyl, 8-quinolyl, and 4-hydroxy-

25 Magidson et al., Arch. Pharm., 274, 74 (1934).
26 Magidson and Grigorovsky, Ber., 69, 396 (1936).
27 Gupta, Iyer and Guha, Current Science (India), 17, 53 (1943).
28 Gupta and Guha, Ibid., 17, 185-6 (1943).
5-quinolyl diguanides were prepared without the terminal $N^5$ isopropyl group. In these cases aryl or hydrogen groups were found in this position. At the present time nothing has been reported in the literature suggesting that these compounds have outstanding antimalarial action. These clinical evaluations often take considerable time.

Wiselogle reports that over two and half times as much 6-methoxy-8-quinolyl diguanide as quinine is required to effect a significant reduction in parasite count in avian malaria.\(^1\)

About the same amount of $N^1\text{-(3-(6-methoxy-8-quinolylamino)propyl)}$ diguanide as quinine is required.\(^1,31\)

As a logical continuation of the research on combining the most potent characteristics of the S-aminoquinoline drugs and those of the diguanide series there is described in this thesis the synthesis of a group of $N^1\text{-}(6\text{-methoxy-8-quinolylamino alkyl)}-N^5\text{-isopropyl diguanides}$ wherein the potent $N^5$ isopropyl diguanide moiety is substituted in place of the terminal amine group in pentaquine and isopentaquine (figures II and III). The alkyl group at $N^1$ is varied to include the ethyl, propyl and butyl constituents as well as the amyl and 1-methylbutyl.

Much work has been done on the introduction of the diguanide 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 a standpoint of the type of compound prepared or the method used.

\(^{31}\) The preparation of this compound could not be found in the literature.
The synthesis of the simple alkyl and aryl derivatives of diguanide has been fairly extensively studied by other workers. The most convenient starting material has been cyanoguanidine. This substance by interaction with ammonium chloride yielded diguanide hydrochloride.\(^{32,33}\) Smolka and Friedreich have extended this reaction to aryl and alkyl amines. The use of ammoniacal copper sulfate seemed to catalyze the reaction with ammonia and allowed the diguanide to be isolated as its sparingly soluble copper chelate.\(^{34,35,36}\) Slotta and Tschesche, showed that cyanoguanidine could be made to react with two molecules of an alkylamine hydrochloride to give a \(N^1, N^5\) dialkyl diguanide.\(^{37}\) They found the reaction took place best by fusion of the two dry solids at 125\(^\circ\). The reaction however soon became exothermic and the temperature rose to 175\(^\circ\), even though the source of heat was withdrawn. Bobeck prepared \(\beta\)-phenylethyldiguanide hydrochloride by fusion of \(\beta\)-phenylethylamine hydrochloride and cyanoguanidine.\(^{38}\) At 150\(^\circ\) he got a 17\% yield; at 160\(^\circ\), 21\%; at 170\(^\circ\), 36.5\%; at 180\(^\circ\), 51.5\%; and at 190\(^\circ\), a optimum yield of 59\%. Sugino and Idzumi prepared methyl

\(^{32}\) Bamberger and Dieckmann, Ber., 25, 545 (1892).
\(^{33}\) Smolka and Friedreich, Montash., 2, 228 (1888).
\(^{34}\) Rathke, Ber., 12, 780 (1879).
\(^{35}\) Herth, ibid., 13, 1358 (1880).
\(^{36}\) Rackmann, Ann., 376, 170 (1910).
\(^{37}\) Slotta and Tschesche, Ber., 62, 1394 (1929).
\(^{38}\) Bobeck, Ann., 487, 294 (1931).
diguanidine hydrochloride by heating methylamine hydrochloride and cyanoguanidine at 128-130°C for 50-60 minutes.\textsuperscript{39}

Tendick and Burckhalter by fusion of p-chlorophenyl cyanoguanidine and benzylamine hydrochloride at 190°C for a minute prepared $N^1$-benzyl-$N^5$-p-chlorophenyl diguanide monohydrochloride in 64% yield.\textsuperscript{40}

Jacobs and Jolles prepared aryl diguanides by heating aryl amines with cyanoguanidine in a medium consisting of a tertiary amine hydrochloride and tertiary amine.\textsuperscript{41} m-Nitroaniline, cyanoguanidine and dimethyl aniline hydrochloride heated at 135°C for 3.5 hours in dimethyl aniline solvent gave $N^1$-(m-nitrophenyl) diguanide hydrochloride.

Aniline, cyanoguanidine and pyridine hydrochloride with pyridine solvent at 135°C gave $N^1$-phenyl diguanide hydrochloride.

King and Tonkin reacted aniline hydrochlorides and cyanoguanidine in refluxing alcohol for 6 hours to prepare good yields of the corresponding aryl diguanides.\textsuperscript{11}

$N^1$-p-Chlorophenyl diguanide was prepared by Curd and Rose, by reacting p-chloroaniline hydrochloride and cyanoguanidine in boiling water for 1 hour.\textsuperscript{42}

$N^1$-p-Isopropyl benzyl diguanide was prepared by Funke and Kornmann by heating 5 g. p-isopropyl benzyl amine, 1 g. cyanoguanidine, 1 g. copper sulfate, and 10 ml. of water in a sealed tube at 120°C for 12


\textsuperscript{40}Tendick and Burckhalter, J. Am. Chem. Soc., 72, 1862 (1950).

\textsuperscript{41}Imperial Chemicals Ind. Ltd., Jacobs and Jolles, British Patent, 587, 907 (May 8, 1947); C. A. 42, 214 (1948).

They also prepared 6-methoxy-8-quinolyl diguanide by reacting 21.5 g. of 6-methoxy-8-aminoquinoline hydrochloride and 8 g. of cyanoguanidine in 40 ml. of boiling water for 1 hour.

Theoretically it seemed possible that diguanides should be capable of synthesis from other starting materials than amine salts and cyanoguanidines and this is supported by the work of Rathke who condensed cyanamide with guanidine and the salts of guanidine to give diguanides, although only in minute yields, and of Schotte, Prieve and Roescheisen who showed that diethylcyanamide will condense with guanidine and guanidine hydrobromide on long standing in alcoholic solution in the cold to give $N^1, N^1$-diethyldiguanide. Cramer found that $N$-phenyl-$N^1$-ethylthiourea reacted with guanidine in the presence of mercuric oxide to yield $N^1$-phenyl-$N^2$-ethyl diguanide. Mercuric oxide acted as a desulfurizing agent.

Almost immediately after the discovery of the chemotherapeutic activity of paludrine a great interest in the synthesis of $N^1$ aryl $N^5$ alkyl diguanides took place. p-Chlorophenyldiguanide was first prepared by Strukov, Sychra and Smirnov and was made by the reaction of p-chloroaniline hydrochloride with cyanoguanidine. Curd and Rose obtained p-chlorophenylycyanoguanidine by coupling cyanoguanidine with p-chlorophenyl diazonium hydrochloride in aqueous sodium carbonate.

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44 Cramer, Ber., 24, 2602 (1901).
to form the triazene, which was decomposed with the elimination of nitrogen by addition to a mixture of concentrated hydrochloric acid and a water-miscible solvent, such as acetic acid or acetone.\textsuperscript{7}

Curd and Rose converted the aryl cyanoguanidines into diguanides by interaction with either the amine hydrochloride or the amine in the presence of copper sulfate. The first method, used mainly with the aromatic amines, was in many cases rapidly completed by using boiling aqueous dioxane or $\alpha$-ethoxyethanol as a solvent. Aliphatic amines, they found, reacted much more slowly under these conditions, and it was more convenient for them to employ the second method with excess of free amine dissolved in aqueous ethanol, with the addition of one equivalent of copper sulfate for each equivalent of cyanoguanidine used. The diguanide was then obtained as a copper complex which in many cases remained in the hot reaction mixture. The rate of conversion into diguanide could be followed by the formation of the colored copper complex. It was found extremely rapid with certain amines, notably secondary amines, but with primary amines a reaction period of from 4 to 24 hours was necessary. In their earliest experiments, the copper chelate was precipitated by the addition of water to the cooled reaction mixture. It was dissolved in dilute hydrochloric acid, the copper precipitated with hydrogen sulfide, and the acid filtrate made alkaline with sodium hydroxide. The use of ammonia instead of sodium hydroxide failed to precipitate many of the strongly basic diguanides. In some cases the sparingly soluble monohydrochlorides were precipitated if the sodium hydroxide was added very slowly. Whenever it was desired to isolate the free base of the
diguanide, the acid filtrate was slowly added with stirring to an excess of sodium hydroxide solution. Curd and Rose also noted that after precipitation of the diguanide copper chelate from the initial reaction mixture, a considerable amount of product remained in the aqueous ethanol filtrate, and the procedure was modified in that either before or after addition of water the excess of ethanol was distilled off, and the resultant suspension was made acid and then worked up without isolation of the copper complex. In one of their experiments copper bronze powder was used in place of copper sulfate. The copper complex was formed as usual as an intermediate and the yield of product was substantially the same.

The synthetic method for diguanides utilizing diazonium salts had too many limitations for a comprehensive exploration of the relationship between antimalarial activity and the many chemical modifications of which diguanides are capable. For example, not all primary aromatic amines could be diazotized and coupled with cyanoguanidine successfully, and the resulting triazenes converted into aryl cyanoguanidines in good yield, and furthermore for the purposes of this research on synthesizing a group of $N^1-(6$-methoxy-8-quinolylaminoalkyl)$-N^5$-isopropyl diguanides the method was not suitable since diazonium salts of alkyl amines are virtually unknown and universally unstable.

Curd, Rose and co-workers$^{15,17,18,19}$ after a rather complete investigation of the cyanoguanidine methods of synthesis of diguanides explored all the alternate routes that had been suggested in the past, and developed some new ones of their own. These explorations did
not develop anything of marked synthetic value that would displace the use of cyanoguanidines but it did give a freedom of choice as to what techniques to utilize in any future synthesis of more than ordinary difficulty.

Crowther, et al. reacted $S$-methyl isothiourea sulfate with isopropyl amine in water to split off methyl mercaptan and yield the isopropyl guanidine salt which was reacted with $p$-chlorophenyl isothiocyanate to yield $N-p$-chlorophenyl-$N^1$-isopropylguanylthiourea. This compound was easily desulfurized in the presence of mercuric oxide and methanolic ammonia to yield paludrine. Conversely, Birtwell, et al. reacted $p$-chlorophenylguanidine with isopropyl isothiocyanate to yield $N-p$-chlorophenylguanyl-$N^1$-isopropylthiourea which was converted with alcoholic ammonia in the presence of lead monoxide to paludrine.

Bami, Iyer and Guha reported the preparation of paludrine by heating $p$-chlorophenylguanidine nitrate with isopropyl cyanamide.

Ainley, et al. also investigated the condensation of alkylcyanamides with arylguanidines and of arylcyanamides with alkyl guanidines. For instance, isopropylcyanamides condensed with $N^1, N^1$-diphenylguanidine and diphenylcyanamide with isopropylguanidine to give $N^1, 1$-diphenyl-$N^5$-isopropyl diguanide. Condensation of $p$-bromophenylcyanamide with methylguanidine gave $N^1-p$-bromophenyl-$N^5$-methyl-diguanide. The most suitable conditions were found to be the interaction of the two substances in boiling butanol, pentanol or toluene solution.

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The successful use of the lower monoalkylcyanamides was surprising on account of their well known tendency to polymerize at elevated temperatures. This polymerization, they found, to be of minor importance, since the yields of diguanide obtained from reactions in which they were used were of the same order as those from the corresponding reactions using the stable dialkylcyanamides. Another contributory factor seemed to be the greater rate of reaction of the monoalkylcyanamides compared with the dialkylcyanamides, maximum diguanide formation being obtained in 15-30 minutes with the mono and only after 2 or 3 hours with the dialkyl compounds. The authors conveniently followed the rate of diguanide formation by taking aliquot samples during the course of the reaction, shaking with standard amounts of ammoniacal copper sulfate and benzene, and comparing the color intensities of the benzene layers; a method developed by Gage and Rose. 47

Funke and Kornmann 22 prepared N°-benzyl-N°-propyl diguanide nitrate by heating an intimate mixture of 0.5 g. of propylguanidine nitrate and 0.5 g. benzyl cyanamide in a metal bath for 2 hours at 130°. The reverse synthesis with isopropylcyanamide and p-isopropyl benzylguanidine nitrate worked equally well.

Ashworth, et al. 19 demonstrated that N°-aryl-N°-alkyldiguanides can be made, although in small yields, by condensing an arylguanidine with an alkylthiourea or by interaction of an arylthiourea with an alkylguanidine. For instance, when p-methoxyphenylguanidine was

condensed with isopropylthiourea in alcoholic solution, in the presence of mercuric oxide, a small yield of \( N^1 \)-p-methoxyphenyl-\( N^5 \)-isopropylbiguanide was isolated as its hydrochloride. Similarly, the condensation of p-chlorophenylthiourea with \( N^1 \), \( N^1 \)-dimethylguanidine gave \( N^1 \)-p-chlorophenyl-\( N^5 \), \( N^5 \)-dimethylbiguanide in about 6% yield.

Birtwell, Curd and Rose, while investigating the Grignard reaction, found that guanidino-magnesium halides reacted with alkyl cyanamides in boiling ether to give complexes which gave diguanides upon hydrolysis. The guanidinomagnesium halides were prepared from the substituted guanidine with ethylmagnesium halide giving a metathesis reaction with evolution of ethane. For example, 1 mole of isopropylcyanamide and 2 moles of p-chlorophenylguanidino magnesium iodide gave a 55% yield of paludrine. 1 Mole of \( N^1 \)-cyano-\( N^3 \)-p-chlorophenylguanidine and 2 moles of isopropylamino magnesium iodide gave approximately a 1% yield of paludrine.

DISCUSSION

Curd, et al. investigated the preparation of alkylo cyanoguanidines and their reaction with arylamines as a method of synthesizing $N^1$ aryl $N^5$ alkyl diguanides. Prior to this investigation no monoalkylcyanoguanidines had been recorded in the literature. Wheeler and Jamieson prepared an alkylo cyanoguanidine by condensing phenyl isothiocyanate with sodium cyanamide to give 1-cyano-3-phenyl-2-sodio pseudo thiourea, which on successive methylation and desulfurization with ammonia gave 1-cyano-3-phenyl-2-methyl pseudo thiourea and 1-cyano-3-phenyl guanidine respectively.  

The condensation of sodium cyanamide with isothiocyanates was first described by Wunderlich, however the correct structure of the products was not given. Hecht studying these reactions was also in error in this respect. Schmidt and Striewsky studied the stability of a series of 1-cyano-3-alkyl-2-alkyl pseudo thioureas they had synthesized. Curd, et al. treated these compounds with ammonia, for example in alcohol at 120°, to eliminate an alkylthiol, and in this way prepared the methyl, ethyl, n-propyl and isopropyl, and n-butyl and isobutyl-cyanoguanidines. May prepared, but did not

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50 Wunderlich, Ber., 12, 443 (1886).
51 Hecht, ibid., 22, 1553 (1890).
52 Schmidt and Striewsky, ibid., 74, 1235 (1941).
isolate or characterize L-cyano-3-isopropylguanidine. Concurrently and independently we have prepared and characterized L-cyano-3-isopropylguanidine by this general synthesis from thioureas and have included this preparation in the experimental section.

In this research cyanamide was first converted into sodium cyanamide in sodium ethoxide solution. The preparation of cyanamide from calcium cyanamide proved to be very difficult and gave only low yields. Carbon dioxide was bubbled through an aqueous suspension of calcium cyanamide and the calcium carbonate filtered off. The cyanamide was obtained by concentrating the solution under reduced pressure. If the solution was heated above 35°C or the pH varied outside the limits of 4 to 5 the cyanamide polymerized rapidly to cyanoguanidine. An experimental sample assaying 65% sodium cyanamide (impurities sodium hydroxide and sodium carbonate) supplied by American Cyanamid Company, was used on one occasion as an alternative to isolating the free cyanamide. When this sample of sodium cyanamide was reacted with isopropyl isothiocyanate in the presence of methyl iodide in alcohol, instead of isolating L-cyano-3-isopropyl-2-methyl-2-thiopseudourrea from the reaction mixture, desulfurization of this product took place in the alcoholic solution. This desulfurization reaction was probably due to the alkaline nature of the impurities in the sodium cyanamide and it resulted in a good yield of a previously unreported compound, L-cyano-3-isopropyl-2-ethyl-2-pseudourrea. This preparation can be found in the experimental section.

53 Private communication, American Cyanamid Company.
Curd, et al. discovered a new preparation of alkylcyano-
guanidines which was a great improvement over the previously discussed
methods. Slotta and Tschesche had reacted sodium dicyanamide with
two molecular proportions of alkylamine hydrochlorides to obtain sym-
metrical $N^1$, $N^5$-dialkyldiguanides. They did not record the inter-
mediate production of alkylcyanoguanidines. Curd, et al. found that
by use of one molecular proportion of an alkylamine hydrochloride,
alanylcyanoguanidines could be prepared, and they stated that the yields
were high, although they did not record the specific yields for each
compound. They effected the reaction in several ways. Thus sodium
dicyanamide and isopropylamine hydrochloride were condensed by heating
them either in a solvent such as butanol or in an aqueous solution of
such a concentration that a temperature of 116-120° was achieved.
Alternatively they prepared the isopropylamine salt of dicyanamide
by double decomposition in water of isopropyl amine and zinc di-
cyanamide and filtration of the zinc hydroxide produced. Evaporation
of the filtrate to dryness and fusion of the resultant hydroscopic
salt at 85° gave them 1-cyano-3-isopropylguanidine. In our work
this compound was prepared in 86% yield from sodium dicyanamide and
isopropyl amine hydrochloride in boiling butanol with the modification
that the unreacted sodium dicyanamide was recovered for future use.
Prepared also by this same general method were two new $N^1$-(6-methoxy-
8-quinolylaminoalkyl)-$N^3$-cyanoguanidines. They were prepared as
possible intermediates in the synthesis of the $N^1$-(6-methoxy-8-
quinolylaminoalkyl)-$N^5$-isopropyl diguanides. Possibly they could
be of chemotherapeutic interest in themselves since the $N^1$-(6-
methoxy-8-quinolyaminocapryl)-guanidines are reported to be only about one sixteenth as toxic as plasmochin.\textsuperscript{54}

Sodium dicyanamide has been made in a number of ways in the past. Madelung and Kern described its preparation from cyanogen bromide and disodium cyanamide, the reaction taking place in aqueous solution and the sodium dicyanamide precipitating out upon evaporation.\textsuperscript{55} Biechler reacted sodium and cyanogen bromide in a ball mill for 60 hours to prepare sodium dicyanamide.\textsuperscript{56} Curd, et al.\textsuperscript{14} found that adding cyanogen bromide to or passing gaseous cyanogen chloride into a solution of commercial calcium cyanamide, making the mixture slightly acid, heating to destroy cyanide produced from a side reaction, and then using the total liquor in subsequent condensations was a successful alternative. Due to the danger and difficulty of the above preparations an experimental sample of sodium dicyanamide was procured from the American Cyanamid Co. and this sample was successfully used in carrying on the research reported in the experimental section of this thesis.

The sodium dicyanamide method of synthesis has also been applied by Curd, et al.\textsuperscript{14} to the preparation of arylcyanoguanidines. This salt reacted more easily with aryl amines than with alkylamines.

Thus with p-chloroaniline hydrochloride in water, the reaction was approximately 80% complete after 24 hours at room temperature, or

\textsuperscript{55} Madelung and Kern, \textit{Ann.}, 427, 1 (1922).
after 7 hours at 50-60°. In addition they condensed the aryloyano-
guanidines with alkylamine hydrochlorides by a new method. Their
previous experience was that refluxing the components together in
aqueous solution gave in general, poor yields of diguanidines, especially
when aryloyano’guanidines were condensed with alkylamine salts which
were sparingly water soluble. They found that when water was re-
placed by an organic solvent such as β-ethoxyethanol, which permits
the reaction to be effected at a higher temperature, good yields of
diguanidines were obtained.

Of the more likely methods of synthesis of N1-(6-methoxy-6-
quinolylaminocalkyl)-N5-isopropyl diguanidines, two seemed upon cir-
cumstances to be the most promising. The N-(6-methoxy-6-quinolyl-
aminocalkyl)-guanidine dinitrates had been synthesized by Drake and
Garman54 and could very likely be condensed with isopropylcyanamide
according to procedures previously mentioned, to give the desired
diguanidines. The work of Ainley, Curd and Rose,15 Funke and Kormann,22
and Basí, Iyer and Gubí,46 however only gave incomplete details
concerning what yields could be expected from this type of reaction.
In addition the N-(6-methoxy-6-quinolylaminocalkyl)-guanidine dinitrates
had been prepared in only 16 to 33% yield from the 8-(aminoalkylamino)–
6-methoxyquinolines. While these yields might be subject to some
improvement it was felt that this proposed synthetic method would
not easily yield 20 to 40 gram samples of the diguanide products for
medical testing.

The second promising method for the synthesis of the desired
diguanidines involved the preparation and use of 1-cyano-3-alkylguanidines.
n the analysis of the data, we observed that the results were consistent with the theoretical predictions. The findings suggest that further research is needed to explore the underlying mechanisms and to develop new applications.

In conclusion, the study has provided valuable insights into the behavior of the studied system. The results have implications for various fields, including physics and engineering, and open up new avenues for future research.
by the different methods gave an undepressed melting point and the
carbon and hydrogen analysis were on the borderline of acceptability
for this compound.

From the results of this experiment it appeared that perhaps
the 1-cyano-3-isopropylguanidine was inactivated in some manner,
either by the presence of the hydrogen chloride from the quinoline
compound, or by the need for a higher reaction temperature, or both.
Consultation of the literature revealed that cyanoguanidine reacted
with hydrogen chloride to form a hydrochloride salt.\textsuperscript{57} Concerning
the reaction temperature, it was known that aromatic amine salts and
cyanoguanidines gave good yields of diguanides in refluxing alcohol.
Numerous experiments reported in the literature indicated that
alkyl diguanides required a somewhat higher temperature than re-
fluxing alcohol would afford, for their preparation.

In any case it was decided next to investigate the reaction
of the free quinoline base with cyanoguanidines. In one experiment
8-(2-aminomethylamino)-6-methoxyquinoline and 1-cyano-3-isopropyl-
guanidine heated between 126-132° in a butyl cellosolve solvent
for 18 hours and then acidified, was worked up to give a good re-
cover of 8-(2-aminomethylamino)-6-methoxyquinoline in the form of
its dihydrochloride salt, undepressed when melting with a known
sample. In this experiment nothing but starting material could be
isolated and characterized. To explain these results one could
assume that the facile reaction of a cyanoguanidine with an amine

\textsuperscript{57} American Cyanamid Company, Nitrogen Chemicals Digest: \textit{The
Chemistry of Dicyandiamide}, 2, 6 (1949), 30 Rockefeller Plaza,
New York.
required the latter to be present as an ion, since most workers in
the past employed amine salts with cyanoguanidines to yield diguanides.

The idea then suggested itself, that the monohydrochloride
separated from the first experiment (when dihydrochloride was used
as a reactant), might react with cyanoguanidines at a higher tempera-
ture to give a diguanide product. Upon further experimentation
this proved to be true.

5-(2-Aminoethylamino)-6-methoxyquinoline monohydrochloride
was prepared by the method of Drake and Garman.\textsuperscript{54} It was heated
at 125-155° with 1-cyano-3-isopropylguanidine in butyl cellosolve
solvent for 3 hours. The reaction mixture was then diluted with a
saturated copper sulfate solution to precipitate a purple copper
complex which was not characterized. By dissolving the complex
compound in hot hydrochloric acid, neutralizing with sodium sulfide,
and filtering off the copper sulfide, an aqueous solution of the
diguanide product resulted, which upon concentrating, precipitated
the \(1^1\)-(2-(6-methoxy-2-quinolyldino)-ethyl)-5'-isopropyl diguanide
monohydrochloride. Further concentration of the filtrate from this
compound gave a precipitate which upon examination proved to be
unreacted 5-(2-aminoethylamino)-6-methoxyquinoline monohydrochloride.

This suggested that the aminoethylamino group in the 5-(2-amino-
ethylamino)-6-methoxyquinoline reactant also formed a complex
compound with copper sulfate as did the diguanide. Although the
copper complex forming tendencies of diguanides had been used
innumerable times in the past by workers to isolate diguanides in
a pure form from reaction mixtures, it appeared that in this
particular synthesis the method was not promising. A control experiment wherein an aqueous solution of 8-(2-aminoethylamino)-6-methoxyquinoline monohydrochloride was poured into a saturated copper sulfate solution gave a precipitate of green copper complex compound. This complex compound was worked up to precipitate the copper as copper sulfide, as explained before, and 8-(2-aminoethylamino)-6-methoxyquinoline dihydrochloride was recovered in the filtrate. Furthermore when the free base, (8-(2-aminoethylamino)-6-methoxyquinoline), 1-cyano-3-isopropylguanidine, and copper sulfate were heated at 145-155° in butyl cellosolve solvent, according to the procedure for free amines developed by Curd and Rose, and the copper complex filtered off and worked up, an almost quantitative recovery of the 8-(2-aminoethylamino)-6-methoxyquinoline as its dihydrochloride took place.

It was to be expected that these difficulties would also apply in the synthesis of the analogous propyl and butyl diguanides which were contemplated since the aminoethylamino and aminobutylamino groups should theoretically also form copper complexes.

From the above experiments it was learned that the desired diguanide compound was formed from 8-(2-aminoethylamino)-6-methoxyquinoline monohydrochloride and 1-cyano-3-isopropylguanidine in the vicinity of 145-155°. The use of the butyl cellosolve solvent, or of any solvent, did not seem necessary in the light of the work of Debeck, Sugino and Imai, Tendick and Burochalter, and others who heated the dry reactants together. This procedure
was more common when alkyl amine hydrochlorides were reacted with cyanoguanidines, but rarely seemed necessary when employing the easily reacting aryl amine hydrochlorides.

Upon further experimentation it was found that the fusion of 1-cyano-3-isopropylguanidine, (m.p. 101-102°), with 8-(2-aminosthylamino)-6-methoxyquinoline monohydrochloride at 170° did not give an easily stirrable reaction mixture. From a theoretical viewpoint good mixing seemed essential for a good yield of product. Raising the temperature resulted in evolution of ammonia from the reaction mixture with resultant decomposition.

Now Curd, et al.\(^{14}\) had shown that 1-cyano-3-isopropylguanidine precipitating from dioxane, crystallized with a half mole of dioxane for every mole of cyanoguanidine. This solvated 1-cyano-3-isopropylguanidine had a melting point of 109-111°. Upon fusion of this material with 8-(2-aminosthylamino)-6-methoxyquinoline monohydrochloride an easily stirrable melt was formed at 170°. It was found that stirring the two components under nitrogen atmosphere for less than an hour at 170° resulted in the reaction mass solidifying so that further stirring was impossible. Assuming that the reaction was completed at this point, recrystallization of the melt from alcohol gave the expected diguanide product, but with a melting point about 10 degrees lower than the analytical sample first isolated utilizing the copper complex method. Furthermore, as to be expected, this low melting material did not give a satisfactory analysis.

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58 Temperatures of all these fusion reactions reported from this point on refer to oil bath temperatures which were in all cases about 10 degrees higher than the internal temperatures of the reaction mixtures.
Many recrystallizations from numerous solvents and solvent pairs only raised the melting point 3 or 4 degrees. In one case after eight recrystallizations, attended with considerable loss of material, the compound still melted 6 degrees low. Use of decolorizing charcoal did not improve the process. The unknown impurity was most likely very similar in physical properties, especially with respect to solubility, to the diguanide. It was known that in chromatography the distribution coefficient is frequently very sensitive to slight differences in chemical structure. The possibility of chromatographic purification strongly suggested itself and at least seemed worth a trial.

Although the list of solvent and adsorbent pairs that could have been tried in chromatography appeared endless, a satisfactory purification occurred luckily in the first trial using an alcohol-benzene solvent and an aluminum oxide adsorbent. It was found in subsequent experiments that the benzene was unnecessary and absolute alcohol as the solvent worked equally well.

The procedure was developed wherein the reaction mixture upon solidification was dissolved in absolute alcohol to form a dark red solution. This solution was allowed to flow by gravity through a column of aluminum oxide, previously saturated with alcohol, until the top of the column was covered with only about a ml. of solution. Elution with alcohol was then started to develop the chromatogram. The diguanide compound colored the entire column pale yellow at the beginning of the elution and passed very easily down the length of the column to give a yellow alcoholic solution when it emerged.
The impurity formed a brown band at the top of the column and upon subsequent elution slowly passed downward. When the brown band was half way down the column the alumina oxide had regained a white hue indicating that very little diguanide was still present in the column and the elution was terminated. In this way about 10 grams of impure material could be purified to yield 8.5 grams of analytically pure diguanide recoverable from the alcoholic solution. The impurity absorbed by the alumina oxide could not be identified.

By the technique outlined above \(N^1-(2-(6\text{-methoxy}-3\text{-quinolylamino})\text{-ethyl})-N^5\text{-isopropyl diguanide monohydrochloride} \) was prepared in 62\% yield. This compound was further investigated to see if the free base could be prepared. The base did not give a satisfactory analysis upon isolation in a strong sodium hydroxide solution. When the base was placed in concentrated hydrochloric acid a salt was isolated that was not the known monohydrochloride. Potentiometric titration of the chloride ion of this salt indicated that a hydrated tetrahydrochloride salt had been isolated. The end point determination and calculations concerning this titration is included in the experimental section. Consultation of the literature showed that Gupta, Iyer and Guha had prepared and identified hydrated trihydrochloride salts of the \(N^1-(3\text{-quinolyl})-N^5\text{-aryl diguanides}\).\(^{27}\) It would be expected that an additional basic group in the 8 amino position of \(N^1-(2-(6\text{-methoxy}-3\text{-quinolylamino})\text{-ethyl})-N^5\text{-isopropyl diguanide} \) existed. The experimental results confirmed this belief.

Preparation of the propyl, butyl, amyl, and 1\text{-methylbutyl} analogs of \(N^1-(2-(6\text{-methoxy}-3\text{-quinolylamino})\text{-ethyl})-N^5\text{-isopropyl diguanide} \)
diguanide monohydrochloride followed the same general procedure outline for the ethyl derivative. In each case the appropriate 8-(aminocalkylamino)-6-methoxyquinoline monohydrochloride was heated and stirred in an inert atmosphere in the presence of an equimolar quantity of 1-cyano-3-isopropylguanidine at a temperature between 150-170° until the reaction mixture solidified and could no longer be stirred. Upon chromatographic purification the yields varied generally between 60 and 70%.

The preparation of the several 8-(aminocalkylamino)-6-methoxyquinolines59 which were isolated first as their dihydrochlorides, and here as their monohydrochlorides followed procedures previously described.

Considerable modification of experimental techniques and improvement of yields resulted in preparing 8-(4-aminol-1-methylbutylamino)-6-methoxyquinoline60 so that the work involved in preparing the 1-aminol-4-bromopentane side chain and the resulting condensation with 6-methoxy-3-aminoquinoline has been included in the experimental section of this thesis.

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Noshor, ibid., 68, 1565 (1946).

In preparing the side chain, $\alpha$-acetobutyrolactone was first prepared from ethylene oxide and acetoacetic ester by the method of Amnyants, Chelintzev and Osetrova.\(^61\) Due to the large quantities of $\alpha$-acetobutyrolactone needed for the synthesis of the side chain, this chemical was later procured from Merck and Co., Inc. This lactone was then refluxed in strong hydrochloric acid solution to yield 1-chloro-4-pentanone by the method of Forman.\(^62\) The 1-chloro-4-pentanone was then reduced to 1-chloro-4-pentanol which was aminated to 1-amino-4-pentanol by the methods of Elderfield, et al.\(^60\)

The reduction of 1-chloro-4-pentanone to 1-chloro-4-pentanol with aluminum isopropoxide was a heat sensitive reaction since with excessive heat and poor temperature control and cooling, the 1-chloro-4-pentanol easily split out hydrogen chloride and cyclized to $\alpha$-methyl tetrahydrofuran. The largest scale that this reduction had previously been performed in with satisfactory yields was a 2± molar run. There is recorded in this thesis a 3.4 molar reduction under somewhat modified conditions, that took place in equal yield. The amination of 1-chloro-4-pentanol was recorded in the literature in 32% yield,\(^60\) but by increasing the ratio of ammonia to chlorohydrin the yield was increased during the course of this research to 38%.

The bromination with thiocynl bromide of 1-amino-4-pentanol to yield 1-amino-4-bromopentane hydrobromide was first performed by Elderfield,\(^60\)

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et al., but without reporting important experimental conditions.
The experimental work in the bromination is included in this thesis
in the interest of future workers in this field.

Of the series of 8-(aminoalkylamino)-6-methoxyquinoline
monohydrochlorides prepared in this research only the 8-(2-aminosteryl-
amino)-6-methoxyquinoline monohydrochloride has been previously
reported. These salts and their preparation from the known
dihydrochloride salts is described in the experimental section.
1-Cyano-3-isopropyl-2-methyl-2-thiopseudouracil. \(^{23}\)

To 500 ml. of an alcoholic solution of sodium ethoxide equivalent to 12 g. (0.52 mole) of sodium was added 27.5 g. (0.65 mole) of cyanamide with efficient stirring and cooling in an ice-bath. Freshly distilled isopropyl isothiocyanate, 50 g. (0.48 mole) was added and the solution was stirred at room temperature for two hours; then 68.5 g. (0.48 mole) of methyl iodide was added and the solution was stirred overnight. It was then concentrated under reduced pressure until all of the solvent was removed. The white crystalline residue was recrystallized from a mixture of 100 ml. of alcohol and 200 ml. of water to yield 66 g. of white needles that melted at 113-115°, (86% overall from the isopropyl isothiocyanate).

1-Cyano-3-isopropylpyrrolidine. \(^{23}\)

(A) From 1-cyano-3-isopropyl-2-methyl-2-thiopseudouracil:

1-Cyano-3-isopropyl-2-methyl-2-thiopseudouracil, 66 g. (0.43 mole) was desulfurized with 680 ml. of 15% alcoholic ammonia at 100° under 150 lbs./in.\(^2\) pressure, for 7.5 hours in a bomb. The bomb contents were decanted into a flask and were concentrated on the steam bath until an oil remained. This oil was diluted with 400 ml. of dioxane and heated on the steam bath until the 1-cyano-3-isopropylpyrrolidine began to crystallize around the edges of the flask. The mixture was diluted to a volume of 500 ml. with dioxane, heated to 85°, and the solution filtered. The filtrate was cooled to 17° whereupon the product precipitated.
It was filtered off and recrystallized twice more from dioxane to which a 0.1 g. of decolorizing charcoal had been added. The yield was 50 g. (68%) of white crystals that had a melting point of 108.5-109.5°, when dried in a vacuum desiccator over paraffin. Each mole of 1-cyano-3-isopropylguanidine crystallizes with a half mole of dioxane.

When dried at 78° in a vacuum oven the melting point was 101-102°. Anal. Calcd. for C₅H₁₀N₄: C, 47.60; H, 7.99; N, 44.41; Found: C, 47.93; H, 7.64; N, 44.68.

(B) From sodium dicyanamide. 63

Isopropyl amine hydrochloride, 68.7 g. (0.72 mole) and 64.3 g. (0.72 mole) of sodium dicyanamide 63 in 185 ml. of refluxing anhydrous butanol were stirred for 3 hours. The cooled solution was filtered and the precipitate was washed with two portions of butanol. The precipitate weighed 51 g. and was extracted with a liter of absolute alcohol in a Soxhlet extractor to reclaim 6.5 g. (0.075 mole) of unreacted sodium dicyanamide for future use. The butanol filtrate and washings were concentrated under reduced pressure until a syrup remained. This syrup when triturated with warm dioxane yielded 105.8 g. (86%) of 1-cyano-3-isopropylguanidine, that melted at 109-111°.

1-Cyano-3-isopropyl-2-ethyl-2-pseudouracil.

Isopropyl isothiocyanate, 139 g. (1.37 moles) and 139 g.

63 Supplied by American Cyanamid Company.
of 65% sodium cyanamide in 600 ml. of absolute alcohol were
stirred at ice-bath temperature for 4 hours. Methyl iodide, 265 ml.
(4.25 moles) was then added with continued cooling and stirring.
The reaction mixture was stirred fifteen hours at room temperature,
then filtered, and the precipitate washed once with absolute alcohol.
The filtrate and washings had a powerful mercaptan like odor and were
allowed to concentrate in a beaker under a hood for three days. The
product began to precipitate at this time, so the solution was diluted
with water and chilled in an ice-bath to yield 127 g. (5%) of white
needles that melted at 67-70°. When recrystallized from aqueous
ethanol the melting point was 70-71°. A qualitative analysis showed
the absence of sulfur. Anal. Calc'd. for: C, 54.17; H, 5.44; N,
27.07; Found: C, 54.12; 54.29; H, 5.54, 5.63; N, 27.05, 26.99.

1-Chloro-4-pentanone.\(^\text{62}\)

Ethylene oxide, 100 g. (2.26 moles) dissolved in a 115 ml.
of chilled absolute alcohol was slowly added with stirring to a
solution of the sodium salt of acetocetic ester (prepared from
305 g. (2.06 moles) of ester, 52 g. (2.26 moles) of sodium, and
900 ml. of absolute ethanol) while cooling in an ice-bath. The
mixture was stirred for 9 hours during which time the reaction
temperature rose to 20° as the ice melted. The alcohol was removed
from the reaction mixture under reduced pressure and the solid
residue was decomposed with dilute acetic acid until the solution

\(^{62}\) Supplied by the American Cyanamid Company. The sample
assayed 65% sodium cyanamide. The impurities were sodium hydroxide
and sodium carbonate.
was neutral to litmus. The aqueous solution was extracted twice with ether and the ether layer was washed with a saturated sodium chloride solution. After the ether layer had been dried over anhydrous sodium sulfate, the ether, alcohol, and unreacted acetoacetic ester were removed from the dried mixture under reduced pressure and the \( \alpha \)-acetobutyrolactone was fractionated. The product weighed 134 g. and boiled at 68-70\(^\circ\)/0.5 mm., (51\% overall from acetoacetic ester).

A solution of 118 ml. concentrated hydrochloric acid, 130 ml. of distilled water, and 134 g. of \( \alpha \)-acetobutyrolactone was heated under reflux in a flask provided with a trap for continuous removal of the product. The reflux was continued until no further 1-chloro-4-pentanone was evolved. The 1-chloro-4-pentanone was separated from the water layer, dried over anhydrous sodium sulfate, and distilled to yield 86 g. of product boiling at 62-63\(^\circ\)/14 mm., (69\% from \( \alpha \)-acetobutyrolactone).

1-Chloro-4-pentanol \[1\]

1-Chloro-4-pentanone, 410 g. (3.4 moles) was added over a period of ½ hour to 2500 ml. of 10 molar aluminum isopropoxide from which the isopropyl alcohol and acetone were being distilled at such a rate as to keep the volume approximately constant. The distillation was continued for 10 minutes longer while dry isopropyl alcohol was added to keep the volume constant. The reaction mixture was then concentrated under reduced pressure to remove as much isopropyl alcohol as possible in 20 minutes. The residue was slowly poured with vigorous stirring into a liter of concentrated hydrochloric acid and 1400 g. of crushed ice which was submerged in an
The addition was regulated so that the temperature did not rise above 50°. The mixture was then centrifuged for 1/2 hour to complete the sedimentation of the gelatinous alumina hydroxide.

The clear supernatant liquid was carefully decanted from the centrifuge tubes and was extracted with five 400 ml. portions of ether. The combined ether extracts were washed with five 300 ml. portions of saturated magnesium sulfate solution. The ether solution was dried over anhydrous magnesium sulfate and the ether and isopropyl alcohol were removed under reduced pressure within a 2 hour period without the temperature exceeding 50°. The residue was dissolved in an equal volume of anhydrous ether, the solution was dried over anhydrous magnesium sulfate, and the solvent removed as before. The 1-chloro-4-pentanol was fractionated and the product weighed 297 g. (71%) and distilled at 46-47°/0.7 mm. During the distillation the temperature of the still pot was not allowed to exceed 85°. The freshly distilled 1-chloro-4-pentanol was stored in the refrigerator and used in the next synthetic step within 4 days.

1-Adam-4-pentanol

1-Chloro-4-pentanol, 250 g. (2.04 mole) was placed in a bomb that was cooled in a dry ice-chloroform mixture. Approximately 2800 ml. (112 moles) of liquid ammonia was introduced into the bomb, which was sealed and allowed to stand at room temperature for five days. The bomb was then vented to allow the ammonia to escape from the reaction mixture. The reaction mixture was decanted into a dilute hydrochloric acid solution. The acid solution was extracted twice with ether to remove 1-chloro-4-pentanol. The acid solution
was then cooled in an ice-bath and potassium hydroxide was added with vigorous stirring until saturated. The aqueous suspension of potassium chloride was extracted with ether five times and the combined ether extracts were dried over potassium hydroxide. The ether was distilled off and the residual amino alcohol was dried and distilled from barium oxide. The product weighed 90 g. (38%) and distilled at 50-51°/0.3 mm. It had a refractive index of \( n_D^{25} = 1.445 \).

1-Amino-4-bromopentane hydrobromide

To 105 g. (1.02 mole) of 1-amino-4-pentanol in 1800 ml. of dry benzene was added dropwise 212 g. (1.02 mole) of freshly distilled thionyl bromide while the mixture was stirred and cooled in an ice-salt bath. The thionyl bromide was added at such a rate that the temperature of the reaction mixture was maintained below 10°. After all the thionyl bromide had been added, the reaction mixture was stirred at a temperature below 10° for 3 more hours. The reaction mixture was then stirred for 5 more hours at room temperature. The 1-amino-4-bromopentan hydrobromide was found as an oil beneath the benzene layer and was separated from the benzene layer. The benzene was evaporated off under reduced pressure to yield additional 1-amino-4-bromopentane hydrobromide which was combined with the first batch separated. The oily 1-amino-4-bromopentane hydrobromide was triturated under a liter of absolute ether until it had crystallized. The light-tan crystals melted below room temperature and were very hygroscopic. They were filtered off rapidly from the absolute ether solution which was cooled to -5°, and stored in a dry Erlenmeyer flask in the refrigerator until used for the next synthetic step.
Efforts to recrystallize the product from various solvents and thereby raise its melting point failed. The product weighed 137 g. and if we assumed it to be pure it would represent 54% of the theoretical yield.

Attempted Synthesis of N²-(2-(6-methoxy-2-quinolylazino)-ethyl)-N⁵-isocrotyl diamide.

(A) From the dihydrochloride:

1-Cyano-3-isopropylguanidine, 3.2 g. (0.025 mole) and 7.3 g. (0.025 mole) of 8-(2-aminioethylamino)-6-methoxyquinoline dihydrochloride were stirred in 32 ml. of refluxing 10% aqueous ethanol for 22 hours. The solution was then cooled and the solvent was removed under reduced pressure leaving a brown precipitate in the flask. Upon recrystallization several times from ethanol a constant melting point range of 205-208° was achieved. The pale-brown crystals were then submitted for analysis. Anal. Found: C, 56.59, 56.36; H, 6.55, 6.60.

8-(2-Aminioethylamino)-6-methoxyquinoline monohydrochloride has the following theoretical analysis. Calc'd for C_{12}H_{15}N_{3}O · HCl: C, 56.76; H, 6.35;

(B) From the free base:

8-(2-Aminioethylamino)-6-methoxyquinoline, 3.3 g. (0.017 mole) and 2.2 g. (0.017 mole) of 1-cyano-3-isopropylguanidine, in 5 ml. of butyl cellosolve were stirred and heated between 125-132° under nitrogen atmosphere for 13 hours. The cooled reaction mixture was acidified with dilute hydrochloric acid and concentrated under reduced pressure until most of the solvent was removed. The residue was diluted and triturated with acetone to give a yellow crystalline
product. When recrystallized once from a water-acetone mixture, 2.4 g. of yellow crystals that melted at 252-254° were recovered. When a mixed melting point with a sample of known 8-(2-aminooethylamino)-6-methoxyquinoline dihydrochloride, melting at 250-252° was taken, no depression was noted.

8-(5-Aminooctylamino)-6-methoxyquinoline monohydrochloride.

The monohydrochloride was prepared from the corresponding dihydrochloride by dissolving the latter in a small amount of water, adding sodium acetate trihydrate until the orange-red colored mixture turned pale yellow at pH 7 and then warming on a steam bath until a solution resulted. The hot solution was filtered and the filtrate was cooled in an ice-bath to precipitate the monohydrochloride. The monohydrochloride was recrystallized twice from absolute alcohol and ether to remove the impurities of sodium chloride and sodium acetate. In this way 26.4 g. (0.065 mole) of dihydrochloride gave 20.5 g. (61%) of monohydrochloride. The yellow crystals melted at 96-97°. Anal. Calc'd for C_{15}H_{21}N_3.Si: Cl, 11.98; Found: Cl, 11.86, 12.01.

8-(4-Aminobutylamino)-6-methoxyquinoline monohydrochloride.

The monohydrochloride was prepared similar to the corresponding amin compound described above. The dihydrochloride, 33.5 g. (0.26 mole) gave 55.4 g. (65%) of greenish-yellow crystals melting at 63-69°. Anal. Calc'd for C_{14}H_{19}N_3.Si: Cl, 12.56; Found: Cl, 12.47, 12.52.

8-(3-Aminopropylamino)-6-methoxyquinoline monohydrochloride.

8-(3-Aminopropylamino)-6-methoxyquinoline dihydrochloride, 26.2 g. (0.086 mole) and 13.2 g. (0.095 mole) of sodium acetate trihydrate and
several drops of water were triturated until the whole mass had liquified. It was then heated on the steam bath for a few minutes, 300 ml. of alcohol was then added and the solution heated to boiling and filtered. The filtrate was cooled in an ice-bath. The resulting precipitate was recrystallized twice from an absolute alcohol-ether mixture to yield 17.0 g. (74%) of pale-tan colored crystals melting at 142-143°. Anal. Calc'd for C_{19}H_{17}OCl: Cl, 13.61; Found: Cl, 13.62, 13.48.

8-(2-Aminoethylamino)-6-methoxyquinoline monohydrochloride.

8-(2-Aminoethylamino)-6-methoxyquinoline dihydrochloride, 36.3 g. (0.13 mole) gave 23.0 g. of monohydrochloride, melting at 207-209°. The light-tan crystals represented 70% of the theoretical yield.

8-(4-Amino-1-methylbutylamino)-6-methoxyquinoline monohydrochloride.

A well stirred mixture of 137 g. (0.555 mole) of 1-amino-4-bromopentane hydrobromide, 193 g. (1.11 moles) of 6-methoxy-8-aminoquinoline and 180 ml. of water was heated continuously for 6 hours at 50°, for 1 hour at 60°, for 1 hour at 70°, and finally for 5 hours at 90-95°. The mixture was diluted with 335 ml. of hot water and then made strongly acid with hydrochloric acid. The acid solution was allowed to cool overnight in an ice-bath. The precipitated salt of 6-methoxy-8-aminoquinoline was filtered and washed twice with ice water. The filtrate was buffered with sodium acetate until neutral to litmus and was then extracted twice with ether to complete the removal of the 6-methoxy-8-aminoquinoline. The aqueous solution from the ether extraction was made strongly alkaline with sodium hydroxide and heated and stirred for 5 hours
at 30° under nitrogen atmosphere. This completed the cyclization of any unreacted 1-amino-4-bromopentane present. The basic solution was then extracted three times with ether and the ether extracts were dried over potassium hydroxide. The ether was distilled off and the 3-(4-amino-1-methylbutylamino)-6-methoxyquinoline\(^6\) was distilled under nitrogen atmosphere at 162-163°/0.01 mm. Some decomposition was noted during the distillation. The drug base was dissolved in benzene and cooled in an ice-bath while hydrogen chloride was bubbled through the solution. The benzene was decanted from the precipitated dihydrochloride which was then washed with several portions of anhydrous ether. The dihydrochloride was stored in a vacuum desiccator since it appeared somewhat hydroscopic. The orange-yellow crystals melted at 207-208°.

The dihydrochloride was triturated with a few ml. of water and enough sodium acetate to give a neutral solution. Approximately 150 ml. of ethanol was added and the mixture was heated on a steam bath for a few minutes. The cooled alcoholic solution was filtered to remove sodium chloride and sodium acetate. The filtrate was diluted to turbidity with ether and cooled in an ice-bath to precipitate tan colored crystals of monohydrochloride. The monohydrochloride was recrystallized twice from a mixture of absolute alcohol and ether to give 17.3 g. (10.6%) of product that melted at 106-107°.

**Analytical Data:**

Calcd. for C\(_{15}\)H\(_{21}\)N\(_3\) \(\cdot\) HCl: Cl, 11.98; Found: 11.84, 11.89.

\(\text{H}^3\)-(5-(6-methoxy-8-quinolylamino)-2-1)-\(\text{H}^3\)-quinoguanidine.

8-(5-aminoanilino)-6-methoxyquinoline monohydrochloride,
11.9 g. (0.04 mole) and 3.6 g. (0.04 mole) of sodium dicyanamide were stirred in 40 ml. of boiling, anhydrous butanol for 3 hours. The cooled solution was filtered to remove the sodium chloride and the filtrate was concentrated under reduced pressure until a precipitate resulted. When filtered off these yellow crystals weighed 9.3 g. They were dissolved in 200 ml. of a mixture of alcohol and benzene (60:40) and poured through an aluminum oxide column. The chromatogram was eluted with 40 ml. of absolute alcohol. The solution was then concentrated under reduced pressure until all the benzene was removed from the alcoholic solution. It was necessary to add some alcohol to the solution during the concentration to remove the last traces of benzene. The final volume was 100 ml. This alcoholic solution was diluted to turbidity with cold water and then cooled in an ice-bath to yield 6.9 g. (53%) of pale-yellow crystals melting at 131-132°. Anal. Calc'd for C_{17}H_{22}O_{6}: C, 62.55; H, 6.79; N, 25.75. Found: C, 62.86, 62.64; H, 6.82, 6.84; N, 25.42, 25.47.

\[
(\text{I}^-\text{-}(2-(6-\text{ethoxy}-6-\text{quinolylamino})-\text{ethyl})-\text{i}^3\text{-cyanoguanidine)}
\]

8-(2-Aminoethylamino)-6-ethoxyquinoline monohydrochloride, 6.5 g. (0.033 mole) and 3.0 g. (0.033 mole) of sodium dicyanamide dissolved in 60 ml. of boiling, anhydrous butanol were heated and stirred for 3 hours. The cooled solution was filtered to remove the sodium chloride and the butanol in the filtrate was removed under reduced pressure. The residue was dissolved in absolute ethanol and water was added to the solution until turbidity

\[65\]

The carbon analysis on these cyanoguanidine compounds usually was high due to unknown reasons.
resulted. Upon cooling a dark colored oil separated which crystallized upon several days standing. These crystals were filtered off and redissolved in 150 ml. of dry ethanol and passed through an aluminum oxide column. The chromatogram was eluted with 10 ml. of absolute alcohol. The alcoholic solution was concentrated under reduced pressure to 50 ml., diluted to turbidity with cold water, and cooled in an ice-bath to yield 3 g. (32%) of pale-yellow crystals, melting at s-161, m. p. 162-163°. *Anal.* Caled for C₁₄H₁₆Cl₆N₆: C, 59.13; H, 5.66; N, 29.56. Found: C, 59.38, 59.47; H, 5.06, 6.05; N, 29.56, 29.44.

H₁-(2-(6-methoxy-3-quinolylaminoc)ethyl)-N₅-isopropyl guanidine monohydrochloride. (U.S. 1910).

Method A 3-(2-Aminethylaminoc)-6-methoxyquinoline monohydrochloride, 4.54 g. (0.018 mole) and 3.05 g. (0.018 mole) of 1-cyano-3-isopropylguanidine were heated and stirred in 15 ml. of butyl cellosolve for 3 hours at temperatures between 145-155°. Approximately 50 ml. of a saturated copper sulfate solution was then added to the reaction mixture with stirring and then the solution was diluted to 250 ml. with water and cooled in an ice-bath. The copper complex of the guanidine product precipitated as pale-purple crystals. These crystals were filtered off and washed twice with water. The copper complex was then dissolved in a hot solution of 12 ml. of concentrated hydrochloric acid and diluted with 250 ml. of water. Powdered sodium sulfide crystals were then added to the solution while stirring until the solution became basic to litmus. A few drops of hydrochloric acid were then added to adjust the pH between 6 and 7. The
resulting copper sulfide precipitate was then filtered off and washed with water. The aqueous filtrate\textsuperscript{66} was concentrated under reduced pressure to 200 ml. whereupon 3.4 g. of pale-green crystals were filtered off which melted at 197-198\(^\circ\). These crystals were recrystallized again from a sodium chloride solution to yield 3.3 g. (48\%) of pale-yellow crystals, m.p. 197-198\(^\circ\). \textit{Anal.} Calcd. for C\textsubscript{17}H\textsubscript{25}Cl\textsubscript{7} · NOCl: C, 53.45; H, 6.89; N, 25.81; Cl, 9.33; Found: C, 53.50, 53.77; H, 6.96, 7.24; N, 25.99, 25.95; Cl, 9.22, 9.33.

\(\text{H}^1\text{-}(2\text{-}(6\text{-methoxy}-2\text{-quinolylamino})\text{-ethyl})\text{-N}^5\text{-isopropyl diaminide monohydrochloride. (U. M. 1917)}\)

\textit{Method B} 2-(2\text{-Aminoethylamino})-6\text{-methoxyquinoline monohydrochloride, 3.0 g. (0.012 mole) and 2.0 g. (0.012 mole) of 1-cyano-3-isopropylguanidine were heated and stirred under nitrogen atmosphere at 168-169\(^\circ\) (oil-bath temperature) for approximately 1 hour at which time the reaction mixture solidified and prevented further stirring, The reaction mixture was dissolved in 60 ml. of absolute alcohol and passed through an aluminum oxide column. The chromatogram was eluted with 15 ml. of absolute alcohol. The alcohol was distilled from the solution while adding benzene at such a rate as to keep the volume approximately constant. When the solution became turbid the distillation was discontinued and the solution was cooled to room temperature allowing the reaction product to crystallize in pale-yellow platlets. The product weighed 2.8 g. (62\%) and melted

\textsuperscript{66}This filtrate when further concentrated yielded a small amount of 8-(2\text{-aminoethylamino})-6\text{-methoxyquinoline monohydrochloride, m.p. 206-209\(^\circ\).}
at 197°. These crystals gave an undepressed melting point with an analytical sample prepared by method A.

**Isolation of the free base of U. M. 1910.**

U. M. 1910, 4.6 g. dissolved in 100 ml. of water was rendered strongly basic with sodium hydroxide (pH 12). The strongly basic solution was heated on the steam bath for 5 minutes and then saturated with sodium chloride and cooled. Tan colored crystals weighing 4.3 g. separated out that melted at 188-189°. This recrystallization process was repeated two more times without change in the melting point. This sample did not give a completely satisfactory analysis for the free base. The degree of hydration was inconsistent. Perhaps a carbonate, bicarbonate, or a half carbonate was formed on standing, but this was not proven by the observed analytical data.

**Preparation of the tetrahydrochloride of the U. M. 1910.**

The free base of U. M. 1910 prepared by the method above was dissolved in a methyl alcohol solution previously saturated with hydrogen chloride. Upon addition of absolute ether a compound precipitated consisting of orange-yellow crystals which decomposed between 116-120°. Repetition of this process produced crystals melting between 118-120°, but further purification attempts did not change the melting point. It was decided that a determination of the number of moles of hydrogen chloride attached to one mole of 3-(2-(6-ethoxy-3-quinolylamino)-ethyl)-8-isopropyl dianine might determine the number of basic positions in this drug. A potentiometric titration using a reference electrode, silver-silver chloride with saturated sodium sulfate bridge; indicator electrode,
metallic silver, was decided upon. Due to the deep-orange color of an aqueous solution of U.S. 1910 a volumetric determination would have a difficulty ascertained end point. A gravimetric determination would be very time consuming.

A 0.3886 g. sample (0.7396 millimoles)\(^{67}\) was dissolved in 100 ml. of distilled water and titrated against a standard silver nitrate solution \((1 \text{ m.e.} = 10.08 \text{ ml.})\). The burette reading at the beginning of the titration was 7.50 ml. and at the end of the titration 37.35 ml. The burette correction was -0.04 ml. This gave a corrected volume of silver nitrate added at the end point of 29.81 ml. which was equivalent of 2.957 milliequivalent of silver nitrate. The milliequivalents of hydrogen chloride per millimole of compound equaled 2.957/0.7396 or 3.998. Therefore, with an accuracy of one part in a thousand we assumed 4 moles of hydrogen chloride attached to 1 mole of \(\text{H}^1\)-(2-(5-methoxy-8-quinolylamino)-ethyl)-\(\text{N}^5\)-isopropyl diguanide. There seemed to be 4 strongly basic positions in the molecule. \(\text{H}^1\)-(5-(6-methoxy-8-quinolylamino)-amyl)-\(\text{N}^5\)-isopropyl diguanide mono-

hydrochloride. (U.S. 2010).

8-(5-Aminoazolylamino)-6-methoxyquinoline monohydrochloride, 15.0 g. (0.051 mole) and 3.6 g. (0.051 mole) of 1-cyano-3-isopropyl-
guanidine were heated and stirred under nitrogen atmosphere at 160-

164° (oil-bath temperature) for 1 1/2 hours. At this point the reaction

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\(^{67}\)Assuming the dihydrate tetrahydrochloride, (molecular weight = 525.35) was formed. For similar salts of diguanides see reference 27.
END POINT DETERMINATION OF POTENTIOMETRIC TITRATION

OF MULTI-HYDROCHLORIDE SALT OF U.M. 1919.
mixture solidified and prevented further stirring. The reaction mass was then dissolved in 250 ml. of absolute alcohol and passed through an aluminum oxide column. The chromatogram was then eluted with 50 ml. of absolute alcohol. The alcoholic solution was concentrated under reduced pressure to 100 ml., diluted to turbidity with absolute ether and cooled in an ice-bath to yield 13.9 g. (62%) of pale-yellow crystals which sintered at 131° and melted at 133-133.5°.

**Anal. Calcd. for C_{20}H_{21}ON_{7} • HCl: C, 56.92; H, 7.6%; N, 23.2%.**

Found: C, 57.05, 57.11; H, 7.87, 7.84; N, 23.01, 23.22.

**1-(4-(6-Methoxy-8-quinolylamino)-butyl)-3-isopropyl diamine non-hydrochloride. (U. H. 2090).**

3-(4-Aminobutylamino)-6-methoxyquinoline monohydrochloride, 13.2 g. (0.0468 mole) and 7.95 g. (0.0468 mole) of 1-cyano-3-isopropyl-guanidine were heated and stirred under nitrogen atmosphere at 150-160° (oil-bath temperature) for 2½ hours at which time the reaction mixture solidified. The reaction mixture was purified as in the previous synthesis to yield 13.6 g. (71%) of pale-yellow crystals, melting at 171°, m.p. 172-173°. **Anal. Calcd. for C_{19}H_{29}ON_{7} • HCl: C, 55.93; H, 7.41; N, 24.03.** Found: C, 56.03, 56.13; H, 7.66, 7.58; N, 24.24, 24.20.

**N^2-(3-(6-Methoxy-8-quinolylamino)-propyl)-N^5-isocrotonyl diamine nonhydrochloride. (U. H. 2090).**

3-(3-Aminopropylamino)-6-methoxyquinoline monohydrochloride, 15.3 g. (0.057 mole) and 9.7 g. (0.057 mole) of 1-cyano-3-isopropyl-guanidine were heated at 170° (oil-bath temperature) under nitrogen atmosphere with efficient mechanical stirring. At the end of 1 hour
the reaction mass had solidified and prevented further stirring. The reaction mixture was purified like the corresponding butyl and amyl diguanides described before, to yield 14.0 g. (62%) of light-yellow crystals, melting at m-211°, m.p. 215-216°. *Anal. Calcd. for C_{18}H_{27}N_{7} • HCl: C, 54.07; H, 7.16; N, 24.89; Found: C, 55.18, 55.00; H, 7.26, 7.32; N, 24.91, 24.87.

N^{4}-(4-methoxy-2-quinolylamino)-1-methylbutyl-5^{5}-isopropyl diguanide monohydrochloride, (U. M. 104/7).

8-(4-amino-1-methylbutylamino)-6-methoxyquinoline monohydrochloride, 11.8 g. (0.04 mole) and 6.8 g. (0.04 mole) of 1-cyano-3-isopropylgeranidine were heated and stirred under nitrogen atmosphere at 150-160° (oil-bath temperature) for 3 hours. At this point the reaction mixture solidified. The reaction mixture was dissolved in 300 ml. of absolute alcohol and passed through an aluminum oxide column. The chromatogram was eluted with 50 ml. absolute alcohol. The alcoholic solution was concentrated under reduced pressure to 100 ml., diluted to turbidity with absolute ether and cooled in an ice-bath to yield 9.0 g. (53%) of yellowish-white crystals, which melted at m-176°, m.p. 177-178°. *Anal. Calcd. for C_{20}H_{31}N_{7} • HCl: C, 56.92; H, 7.64; N, 23.29; Found: C, 57.15, 56.95; H, 7.35, 7.33; N, 22.98, 23.28.
ABSTRACT

Raymond J. Kray, Ph. D., 1951 (S. S. Villanova College)
Title of thesis: The Synthesis of $N^1$-(6-methoxy-8-
quinolylaminoalkyl)-$N^5$-Isopropyl Diguanydines and Intermediates.
Thesis directed by Dr. Nathan L. Drake
Major: Organic Chemistry
Minor: Physical and Inorganic Chemistry

This paper describes the preparation and properties of seven
potential antimalarial drugs. These may be divided into two classes:
(1) $8$-(aminoalkylamino) quinoline derivatives of cyanoxuanidine,
and (2) $8$-(aminoalkylamino) quinoline derivatives of isopropyl
diguanydine. The first class of compounds was prepared by condensation
of sodium diyuanidine with the appropriate $8$-(aminoalkylamino)
quinoine monohydrochloride in butanol solvent. The second class
of compounds was prepared by heating the appropriate $8$-(aminoalkyl-
amino) quinoline monohydrochloride with 1-cyano-3-isopropylguanidine
without solvent. The preparation of a number of intermediate compounds
and salts which are also new is described as are the syntheses of a
series of known compounds which have been prepared by new or improved
methods.

The following new compounds have been prepared: $N^1$-(2-(6-
methoxy-8-quinolylamino)-ethyl)-$N^3$-cyanoxuanidine, $N^1$-(5-(6-methoxy-
8-quinolylamino)-aryl)-$N^3$-cyanoxuanidine, $N^1$-(2-(6-methoxy-8-quinolyl-
amino)-ethyl)-$N^5$-isopropyl diguanide monohydrochloride, $N^1$-(3-(6-
methoxy-8-quinolylamino)-propyl)-$N^5$-isopropyl diguanide monohy-
drochloride, $N^1$-(4-(6-methoxy-8-quinolylamino)-butyl)-$N^5$-isopropyl
diguanide monohydrochloride, \( N^1-(5\text{-}(6\text{-methoxy-8\text{-quinolylamino})\text{-amyl}) \)
-\( N^5\text{-isopropyl diguanide monohydrochloride, } N^1-(4\text{-}(6\text{-methoxy-8\text{-quinolylamino})\text{-1-methylbutyl}) \)
-\( N^5\text{-isopropyl diguanide monohydrochloride and 1-cyano-3-isopropyl-2-ethyl-2-pseudouracil.} \)

Incidental to the preparation of the above compounds a number of new salts of the 3-(aminocalkylamino)-6-methoxyquinolines have been described, namely: 3-(3-aminopropylamino)-6-methoxyquinoline monohydrochloride, 3-(4-aminobutylamino)-6-methoxyquinoline monohydrochloride, 3-(5-aminocetylamino)-6-methoxyquinoline monohydrochloride, and 3-(4-amin-1-methylbutylamino)-6-methoxyquinoline monohydrochloride.

Improvements in yields or in experimental techniques in the preparation of the following intermediates have been made: 1-chloro-4-pentanone, 1-chloro-4-pentanol, 1-amino-4-pentanol, 1-amino-4-bromopentane hydrobromide, 1-cyano-3-isopropylguanidine, and 1-cyano-3-isopropyl-2-methyl-2-thiopseudouracil.

A discussion is also included on the preparation, isolation, purification and salt formation of the \( N^1-(6\text{-methoxy-8\text{-quinolylamino})\text{-aminoalkyl}) \)-\( N^5\text{-isopropyl diguanides.} \)
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