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SYNTHETIC ANTIMALARIALS

By

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fulfillment of the requirements for the
degree of Doctor of Philosophy

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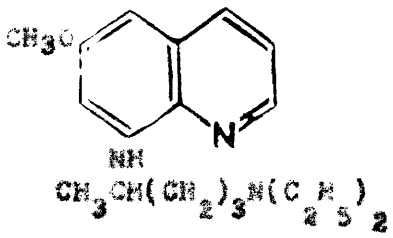
INTRODUCTION

During the course of the recent government sponsored antimalarial research program[1] more than 15,000 preparations were tested for antimalarial activity. A study of the collected results[2] of this work brings to light the fact that of the numerous types of compounds studied many of the potentially most useful drugs are either 4- or 8-aminoquinolines. Prior to the above mentioned activity in the field of antimalarials, these types of quinolines had been investigated in both Germany and Russia. A notable result of these earlier studies is to be found in Plasmochin (pamaquine)[3] , 8-(4-diethylamino-1-methylbutylamino)-6-methoxyquinoline (SN-971)[4], which has been reported to effect a cure of vivax malaria



I

when administered along with quinine. Of the 4-aminoquinolines, 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline (SN-7618)(II), a

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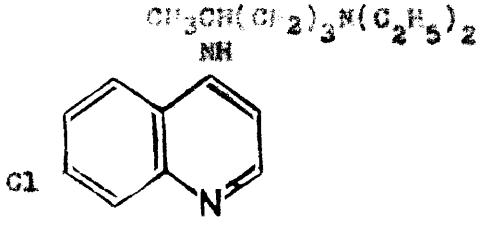
[1]The work carried out during the recent emergency under contracts recommended by the Committee on Medical Research between the Office of Scientific Research and Development and various research organizations and educational institutions.

[2]F.Y. Wiselogle, A Survey of Antimalarial Drugs 1941-1945(Ann Arbor, Michigan: J. W. Edwards, 1946.).

[3]Schulemann, Schönhöfer and Wingler, U. S. Patent 1,747,531 (1930).

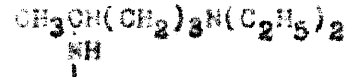
[4]The survey number (SN) identifies the drug in the monograph. See[2] .



II

compound which received considerable attention during the present program,[5] has been described earlier in the patent literature[6] and more recently by Surrey and Hammer.[7] At the present time, SN-7618 is probably considered the most useful of the members of this type of drug in view of its effectual use as a suppressive in the control of malaria. As a consequence of the favorable activity of SN-7618, a study of variations in both the quinoline nucleus as well as the alkylaminoalkylamino side chain was undertaken early in the program. The chemistry of most of these investigations has already been reported in the literature.[8] The first part of this paper is concerned with the continuation of a study of a particular variation in the structure of the side chain.

The side chain of SN-7618 (III) contains two basic nitrogen atoms



III

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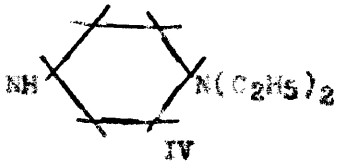
[5]Drake, Creech, Draper, Herman, Haywood, Peck, Selton and Van Hook, J. Am. Chem. Soc., 68, 1214 (1946).

[6]Andersag, Breitner and Jung, U.S. Patent 2,233,970, March 4, 1941.

[7]Surrey and Hammer, J. Am. Chem. Soc., 68, 113 (1946).

[8]Most of these papers appear in J. Am. Chem. Soc., 68 (1946)

separated by a straight chain of four carbons. The replacement of the tetramethylene group by a 1,4,-cyclohexylene group would maintain essentially the same features except that the basic nitrogen atoms would now be separated by two four-carbon chains.



IV

The compound, 7-chloro-4(4-diethylaminocyclohexylamino) quinoline (SN*12,108 and 14,477)[9] was prepared[10] and found to be sufficiently active to warrant further efforts along these lines. It was observed that the product obtained in the preparation of 7-chloro-4-(4-diethylaminocyclohexylamino) quinoline consisted of a mixture of the cis and trans isomers possible in view of the presence of the disubstituted cyclohexane portion of the side chain. The cis (SN-12,108) and trans (SN-14,477) forms have been separated by a tedious process of fractional crystallization. As reported by Todd,[11] the relative proportions of the cis and trans forms in 4-diethylaminocyclohexylamine and, therefore in the product is affected by the catalyst and the method of hydrogenation used in the preparation of the diamine from its corresponding benzenoid precursor.

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[9]The reason for two SN number becomes apparent later.

[10]Drake, Creech, Garman, Haywood, Peck, Van Hook and Walton, J. Am. Chem. Soc., 1206 (1946).

[11]Behr, Kirby, MacDonald and Todd, ibid. 68, 1296 (1946).

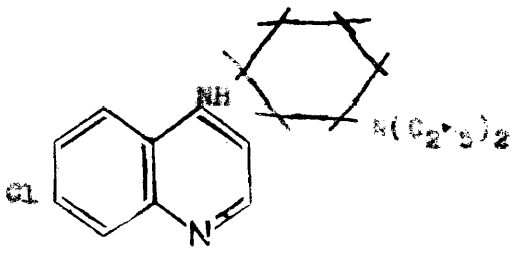
The higher melting trans form(m.p. 223-225.5°) was easily separated from the crude reaction product in all cases. However, the lower melting cis form was isolated, with no little difficulty, only from a coupling product wherein 4-diethylaminocyclohexylamine containing a larger proportion of the cis modification was used. Attempts to obtain the cis modification from reaction mixtures not having a favorable proportion of the lower melting form led to the isolation of a constant melting (m.p. 147-149°) fraction which was arbitrarily designated as a eutectic mixture of the cis and trans modifications.

It seemed desirable, to establish definitely which of the lower melting fractions was the pure stereoisomer and which the apparently inseparable mixture of both modifications. To this end samples of all three fractions were subjected to the counter-current distribution analysis as described by Craig.[12a,b,c,d,e,f]

The results of these analyses, which appear in detail later in this paper, clearly bear out the original suppositions. The fractions which melt at 157.8-159° and 223-225.5° are within a few percent pure individual isomers, while the fraction which melts at 147-149° is a mixture of the above in the approximate ratio of 60 percent cis and 30 percent trans. Testing data seem to indicate that the trans form (SN-14,477) may be slightly more active as an antimalarial than the corresponding cis modification (SN-12,108).

[12a] Craig, J. Biol. Chem. 150,33 (1944).
[b] Craig, et al., ibid. 155,519 (1944).
[c] Craig, et al., ibid., 161,321 (1945).
[d] Craig, et al., Science, May, 1946.
[e] Williamson and Craig, J. Am. Chem. Soc. (in press).
[f] Williamson, Holley and Galbreath, (private communication).

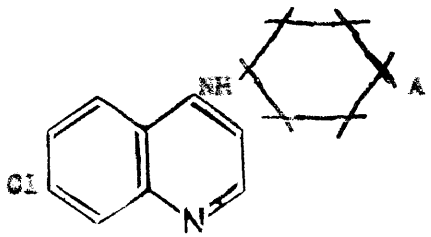
A further modification of the side chain involved the preparation[8] of 7-chloro-4(3-diethylaminocyclohexylamino) quinoline (SN-12,107)(V) wherein the two basic nitrogens of the side chain are no longer separated



V

by straight chains of four carbon atoms. SN-12,107, although active, was not quite as active as SN-14,477. For this reason it was decided that further variations in structure should be carried out in compounds related to SN-14,477 rather than SN-12,107.

To this end six compounds, the subject of part of this thesis having the general structure (VI), were prepared. These compounds are



VI

listed in Table I. Their preparation, like that of SN-7618,[5] involved the amination of 4,7-dichloroquinoline[13] with an appropriate diamine. The preparation of these diamines is described elsewhere.[11]

Certain of the aminations (commonly referred to as couplings) could be carried out satisfactorily only when phenol was used as a solvent.

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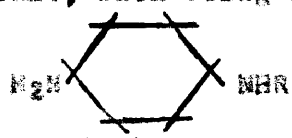
[13] Hereinafter designated DCQ.

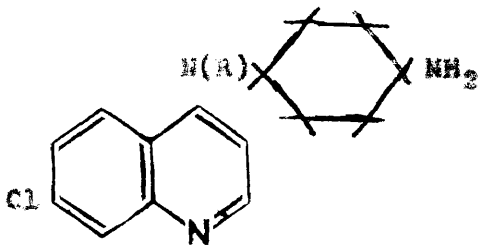
One attempt to couple DCQ with 4-cyclohexylaminocyclohexylamine without using phenol failed to go to completion even after nine hours of heating. About one-third of the DCQ was recovered unchanged.

Completion of a coupling reaction was determined by means of one of the following testing procedures. A small portion of the reaction mixture was dissolved in five percent nitric acid. Upon the addition of concentrated sodium acetate solution, the appearance of a white precipitate indicated the presence of unreacted DCQ. The absence of such a precipitate was taken as evidence of a completed reaction. Sometimes the test sample of the reaction mixture was not completely soluble in dilute nitric acid, probably because the salts of the drugs in these cases were only sparingly soluble in dilute acid. Filtration, to remove this insoluble material yielded a clear filtrate which was usually responsive to testing with concentrated sodium acetate solution. When phenol had been used as a solvent in the coupling, the above testing schemes were of little value. In these cases solubility of a drop of the reaction mixture in dilute acetic acid was used to determine a completed reaction. The temperatures used in the coupling reactions were arrived at by noting that temperature at which the reaction becomes sufficiently exothermic to maintain an internal temperature slightly higher than the bath temperature. This method has been described previously[8] for reactions involving similar reactants.

It should be noted that, when using side chains of the type



there is a possibility that alkylation might occur on the secondary nitrogen, and compounds (VII) of entirely different structure would be



VII

the result. However, the experience of other investigators[14,15] working with similar side chains makes it appear that such a reaction would be highly improbable.

When the coupling reactions were complete, the products were obtained from the crude reaction mixtures by procedures very similar to those used previously.[9,10] Of course, variations in these procedures were necessary in most cases. The details of the methods used are presented in the experimental section.

As was found in the case of 7-chloro-4(diethylaminocyclohexylamino) quinoline, the products obtained were mixtures of the possible geometric isomers. As the trans or higher melting form of the above compound was found to be slightly more active than the cis modification, only the easily separable high melting forms of these six new compounds were fractionated from residual (and difficulty separable) mixtures of the cis and trans forms.

Plasmochin (pamaquine), as mentioned before, was of special interest because it was reported to be able to effect a cure of vivax malaria

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[14] Tarbell, Shakespeare, Claus and Bunnett, J. Am. Chem. Soc., 68, 1217 (1946)

[15] Pearson, Jones and Cope, ibid., 68,1225 (1946)

when administered in sufficiently high dosage along with quinine. However, the dosage of Plasmochin required to produce this desirable effect is also approximately the maximum tolerated dose; an unfortunate circumstance which limits the routine clinical use of this drug. The high toxicity of Plasmochin prompted an intensive investigation of other related 8-aminoquinolines in the hope of finding a drug possessing similar curative action and lower toxicity.

Of the numerous compounds studied, Pentaquine, 8-(5-isopropylamino-amylamino)-6-methoxyquinoline (SN-13,276)[16] appeared to be most promising.[17] In clinical trials it was shown to be capable of preventing the characteristic relapses of vivax malaria. However, like Plasmochin (though to a lesser extent), it caused toxic reactions in some cases when the dosage was high enough to insure prevention of relapses. With reduction of toxicity and retention of activity the purpose, variations in the structure of SN-13,276 were carried out. The remaining portion of this thesis will describe some of these variations. Others have been previously reported in part.[18]

In 1942 patents were taken out on a drug called Certuna, 8-(3-dimethylamino-1-methylpropylamino) 6-quinolinol (SN-191) (VIII).[19]

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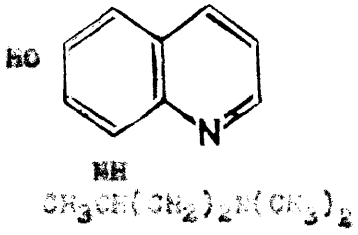
[16] Drake, et al., Ibid., 68,1129 (1946)

[17] Another compound 8-(4-isopropylamino-1-methylbutylamino)-6-methoxyquinoline (SN-13,274) has also produced favorable results in clinical trials. Cf. Elderfield, et al., J. Am. Chem. Soc., 68,1524 (1946).

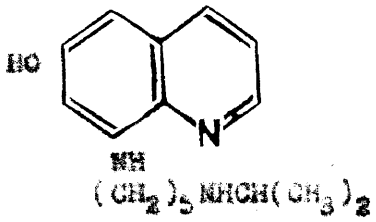
[18] Many publications describing this work are to be found in: J. Am. Chem. Soc., 68, (1946).

[19] Kikuth, U. S. Patent 2,291,235, July 28, 1942.



VIII

The name, Certuna, appears to have been a rather unfortunate choice in view of the drugs ineffectiveness as an antimalarial. However, it was observed that Certuna could be tolerated by humans in much larger doses than either Plasmochin or Pentaquine without causing disturbing toxic reactions. With the above data in mind the quinolinol (IX) corresponding to UM-13,276 was prepared for testing.[16] As the results in



IX

preliminary tests were encouraging, an additional quantity of 8-(5-isopropylaminoamylamino)-6-quinolinol (UM-132,) (SN-15,324)[20] was required

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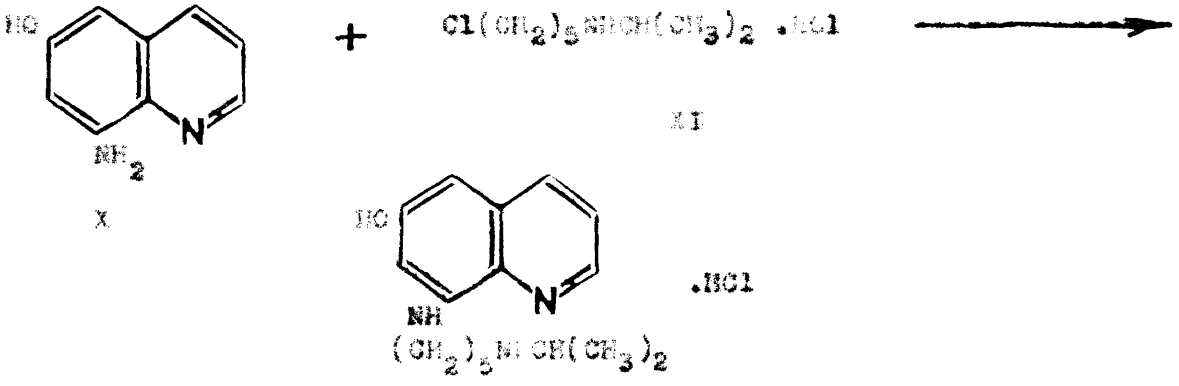
[20] The University of Maryland number (UM) is used to identify compounds mentioned in this paper which were tested after the Survey Office closed. Testing results obtained for these compounds are not to be found in the monograph[2] but were secured from private reports of the present testing organizations. Testing data made available since the close of the Survey Office are included in Tables VII, VIII. Some of the compounds referred to by UM number have recently been assigned SN numbers which are a continuation of those used in the monograph. These new SN numbers have been included here as aids to identifying these compounds in further testing publications which will undoubtedly use the SN designation.

for clinical testing and toxicity determinations. The first samples of UK-1228 were prepared by the demethylation of SN-13,276 using aqueous hydriodic acid. Briefly, the demethylation procedure, reported previously,[16] involved heating a free base of SN-13,276 in an excess of constant boiling hydriodic acid. The excess acid was then removed at reduced pressure and the residue was dissolved in water. Neutralization of this acid solution with sodium bicarbonate followed by extraction with chloroform led to the eventual preparation of a pure salt from the crude free base; the base itself was not isolated. The low yield (38-percent) of product obtained using this procedure initiated a search for an improved method of preparing UK-1228. In addition to the demethylation procedure, UK-1228 should be produced in the coupling of 8-amino-6-quinolinol (X) with 1-chloro-5-isopropylaminopentane hydrochloride (XI) as shown in the equation.



The patent literature claims this method can be applied to the preparation of Certuss. However, the results in a similar reaction involving (X) and 5-diethylaminoamylbromide hydrobromide instead of

(XI) were so discouraging that this method was abandoned. Demethylation of SN-13,276 was again considered in the hope that the yield could be improved. It was decided to use constant boiling hydrobromic acid instead of hydriodic acid because aqueous hydriodic acid solutions are rather unstable and require redistillation immediately before use. In addition it had been assumed by other workers that the low yields of product obtained in demethylations employing hydriodic acid were caused by excessive cleavage of the side chain from the nucleus. It was hoped that hydrobromic acid might be less drastic in its action in this respect.

In a preliminary trial, the free base of SN-13,276 was heated with excess hydrobromic acid, after which the excess acid was removed by distillation at reduced pressure. The residue was dissolved in water and neutralized with sodium hydroxide solution to the end that the free base of UM-122Q might be extracted into a suitable solvent. However, at about pH 10 a pasty mass had separated from solution. This material rapidly solidified. Eventual purification of this solid through crystallization and sublimation yielded a product which analyzed for the free base of UM-122Q. In addition, the free-base could be converted to a dihydroiodide whose melting point checked that of previously prepared samples of this salt of UM-122Q. The fact that the free base of UM-122Q was a solid had not been observed by the previous workers, and it was thought that the isolation and purification of this solid free base before conversion to a salt would supply a means of improving the yield of the demethylation reaction. By operating in this manner it was possible to obtain the pure salts of UM-122Q in yields of 60-70 percent which represents a considerable improvement over those previously obtained.

Further work along these lines indicated that extensive purification of the free base was unnecessary. The only improvement accomplished by the numerous recrystallizations at this stage is the removal of a small but persistant amount of colored impurity with the accompanying loss of considerable amounts of the product. It was discovered that the salts prepared directly from the crude free-base were identical to those prepared from carefully purified free base. Apparently the colored impurity is quite effectively removed during the preparation of the salt. With this information at hand, three general methods were finally worked out for the preparation of the dihydrobromide salts of UM-122Q in yields of about 90 percent. These procedures, one of which uses sulfuric acid in place of hydrobromic acid, will be described in detail in the experimental section of this paper.

Some of the properties of UM-122, are interesting. As mentioned before the free base can be readily sublimed, and after sufficient purification, sublimation yields a pale yellow solid which is apparently rather stable. However, samples of the free base which have not been carefully purified darken rapidly during storage. This decomposition is probably due to oxidation. The salts of UM-122Q are far more stable than the free base, and samples of the dihydrobromide have not changed noticeably over a period of six months. As observed in the case of salts of other 8-aminoquinolines, the salts of UM-122, and two equivalents of acid are more soluble in water and less soluble in alcohol than the corresponding mono-salts.

In addition to forming salts with acids, UM-122, also forms a sodium salt. The sodium salt is very unstable and all attempts to purify a sample for analysis were unsuccessful. It can be isolated by adding

an aqueous solution of the dihydrobromide to an excess of 10 percent sodium hydroxide solution from which the sodium salt separates. When this operation is carried out using five percent alkali or less, the sodium salt remains in solution.

The methods used in preparing UM-122, have been applied in the preparation of 8-(5-diethylaminoamylamino)-6-quinolinol (UM-157), a compound needed as the starting material in another phase of this work. The precursor of UM-157, is 8-(5-diethylaminoamylamino)-6-methoxyquinoline (SN-12,904). Although the preparation of this compound appears in the literature,[21,22] an account of the coupling reaction used in the present preparation is included in the experimental section as the yield (72 percent) represents a considerable improvement over that (19 percent) reported previously.

Two other quinolinols, 8-(5-aminoamylamino)-6-quinolinol (UM-175,) and 8-(4-isopropyl-1-methylbutylamino)-6-quinolinol (UM-173,) were also prepared from the corresponding 6-methoxyquinolines. Although the yields in these two preparations were far from being satisfactory, it was decided that attempts to work out improvements were unnecessary at this time. In addition to the above quinolinols, 8-(4-diethylamino-1-methylbutylamino)-6-quinolinol was prepared by the demethylation of Plasmochin with hydriodic acid.

Although the preliminary testing of UM-122, yielded interesting results, clinical trials were disappointing. Even when administered in the larges doses which could be tolerated, UM-122, did not ef-

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[21] Elderfield, et al., J. Am. Chem. Soc., 68,1524-9 (1946).

[22] Magidson and Strukov, Arch. Pharm. 271, 569 (1933).

fectively prevent relapses. In addition to possessing low activity, the drug is also much less toxic than the corresponding 6-methoxy derivation (SN-13,276). Incomplete biochemical investigations yielded scanty evidence upon which were based some theories as to the fate and possible action of the 8-aminoquinolines in man.[23] These ideas, correct or not, prompted attempts to prepare derivatives of UM-1224 in which the hydroxyl was part of an ester linkage.

UM-1224 has, in addition to the phenolic hydroxyl, two secondary amino groups which are capable of forming amides in a reaction directed toward acylation of the phenolic hydroxyl. In fact, it would be expected that the aliphatic amino group at the end of the side chain would react more readily than the phenolic hydroxyl. For this reason it was decided to initiate these studies using a quinolinol which possessed a tertiary, and therefore unreactive, terminal amino group. 8-(5-Diethylaminoamylamino)-6-quinolinol, (UM-1574), the preparation of which is described herein, was chosen as the starting material because of its structural similarity to UM-1224.

Schönhöfer[24] has reported the acetylation of 8-(4-dimethylamino-1-methylpropylamino)-6-quinolinol, Certuna, (SN-191) using two methods, one of which led to the acetylation of the phenolic hydroxyl (XII) while the other yields the product (XIII) of N- acetylation. Although

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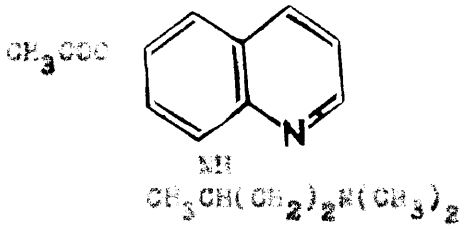
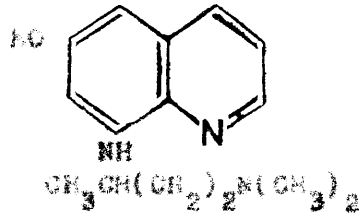
[23]Private communications. It is believed unnecessary to describe this biochemical work and the reasoning based on it in this paper. It was mentioned merely to indicate a motive for continuing work along these lines.

[24]Schönhöfer, A. Physiol. Chem., 274, 1 (1942).



XII



XIII

Schönhöfer's paper is almost devoid of experimental detail, it does mention that O-acetylation is accomplished when pyridine is the solvent, and that N-acetylation is carried out in methylene chloride.

With this information at hand UK-1497 was successfully acylated, presumably on the phenolic hydroxyl, using acetic, benzoic and p-chlorobenzoic anhydrides as the acylating agents and pyridine as the solvent. The corresponding esters were obtained in fairly good yield from reactions carried out at room temperature over extended periods of time using one molecular equivalent of the acylating agent. The time necessary to complete these reactions varied from twenty-four hours in the case of the acetate to seven days for the p-chlorobenzoate. The time of reaction was, roughly, the time necessary for a mixture of the reactants to become completely homogeneous.[25]

The esters were isolated from the reaction solution by the addition of alkali followed by extraction with chloroform. This procedure must be carried out rapidly and at ice temperature as the products are readily hydrolyzed in the alkaline medium. The crude esters were purified further by distillation at reduced pressure in a Hickman pot type molecular still. The distilled products were obtained as viscous,

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[25] In the case of the p-chlorobenzoate small amounts of solid were still present even after a period of seven days.

yellow oils which were readily converted into crystalline salts. The purification of these salts, requiring many recrystallizations, was a tedious process.

No positive proof that O- rather than N-acylation occured in the above reactions has been obtained. However, the following observations make it seem likely that the above compounds are the desired esters of the phenolic hydroxyl. Schönhöfer reported the acetate of Certuna to be a liquid while the corresponding N-acetyl derivative was a white solid melting at 182°. The free bases of all the acylated compounds herein described are also liquids. The ferric chloride test for the phenolic hydroxyl group was carried out on a number of quinoline derivatives including UK-122, and related quinolinols, various 6-methoxyquinolines, as well as the acylated derivatives in question. When testing was carried out under similar conditions, the colors obtained with the quinolinols were much deeper and more characteristic of a positive phenol test than those obtained for the acylated derivatives and the 6-methoxyquinolines. However, it should be noted that the results of a ferric chloride test on compounds which are already rather colored and contain additional functional groups cannot be considered conclusive. Another point in favor of the proposed structure of these compounds is the apparent absence of the acidic properties which should accompany a phenolic hydroxyl if it were present. UK-122, is readily soluble in dilute alkali as previously mentioned. The acylated derivatives of UK-157, are not soluble under similar conditions. Finally Barber and Bragg[26] have reported that the aniline nitrogen of Plasmochin (pamaquine) is not acetylated by acetic anhydride in pyridine.

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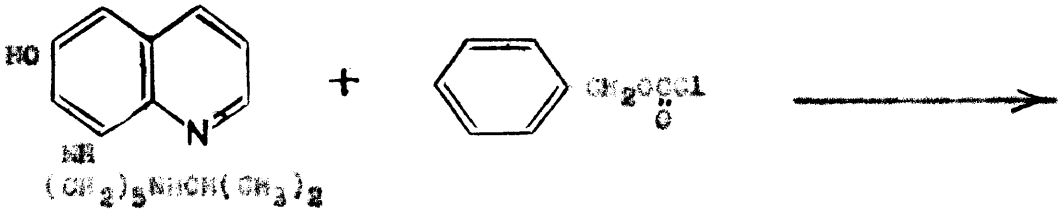
[26] Barber and Bragg, J. Chem. Soc. 1946, 610.

The method used for acetylating UM-157$_6$ proved to be entirely unsuccessful when applied to UM-122 . Apparently the reactive amino group in this case is acetylated more rapidly than the phenolic hydroxyl. It became apparent that perhaps an indirect method of synthesis would be useful in attaining the end in view. Acetylation of an intermediate in which the reactive amine was covered by a suitable blocking group, followed by the removal of the blocking group seemed to be a logical approach.

Because of the labile nature of the quinolinol esters, the blocking group used in such a series of reactions should be one whose removal could be carried out under rather mild conditions. Carbobenzoxychloride (XIV), a reagent which has been successfully used in protecting amino groups in the preparation of various synthetic polypeptides,[27] appeared to be suitable for the present work. Removal of the carbobenzoxy group is usually done by low pressure hydrogenation at room temperature using a palladium catalyst. The proposed synthesis is outlined in the following series of reactions.



XIV

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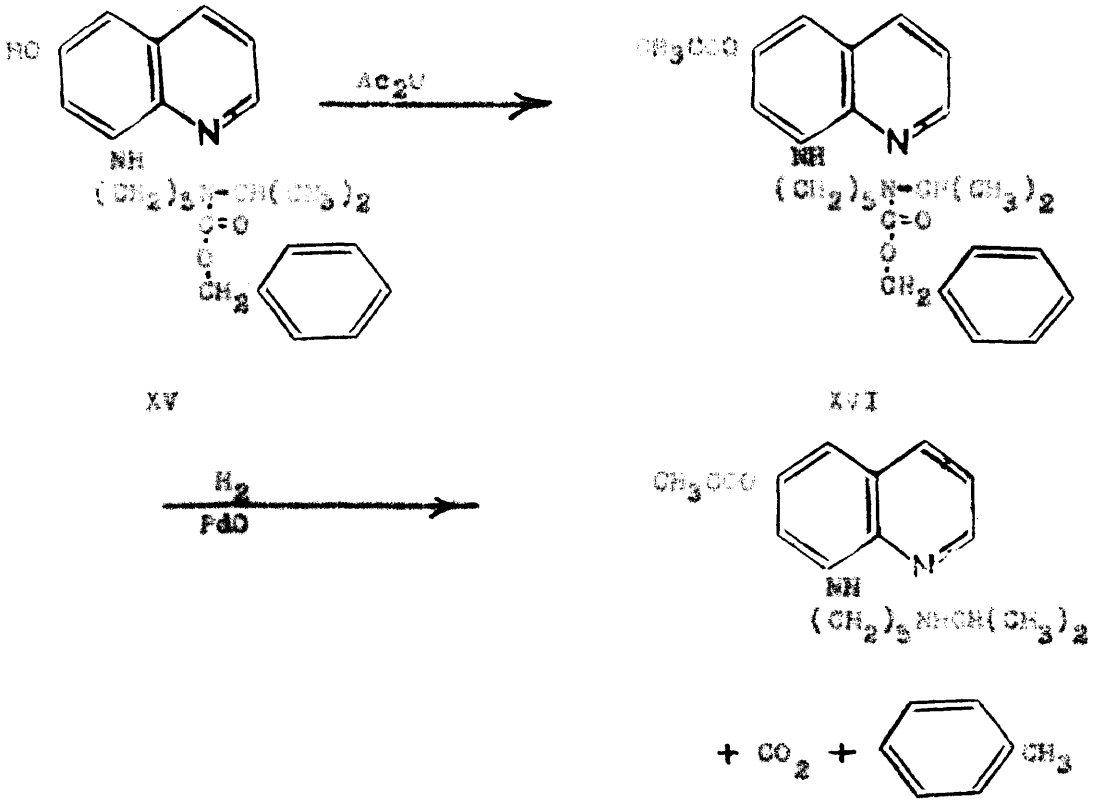
[27] Bergmann and Zervas, Ber., 65, 1192 (1932).



XV XVI

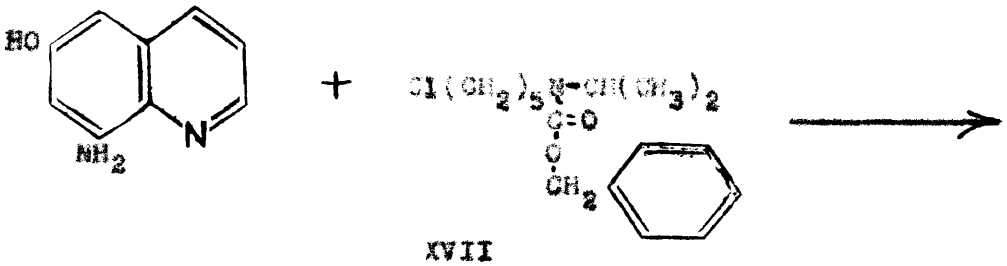
It was expected that (XV) would be a solid, however, the product obtained from several reactions was an oil which could not be characterized. Attempts to purify (XV) by molecular distillation failed in that it decomposed badly before the distillation temperature could be attained. Likewise (XV) would not form a crystalline salt. Although little could be learned concerning the nature of this intermediate, it was decided to proceed using the crude oil in the next step. Acetylation of crude (XV) was carried out with acetic anhydride in pyridine. As in the previous step, the product from this reaction could not be characterized. Reduction of this crude intermediate (XVI) yielded no identifyable products.

The failure of the above series of reactions to produce the expected compound may be attributed to any of a number of reasons. Those which appeared to be most likely include, (1) simultaneous reduction

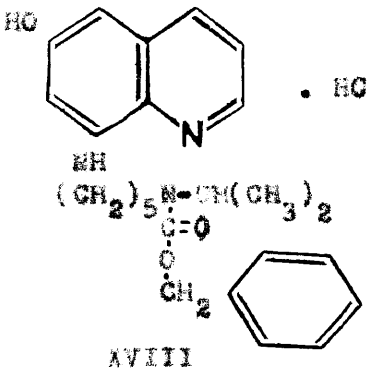
of the quinoline nucleus during the hydrogenation step; (2) reaction of the blocking reagent with functional groups other than the aliphatic secondary amine and (3) failure of the hydrogenation to remove the blocking group. Only the first of the above reasons was definitely eliminated as a possible deterrent in the above scheme. This was demonstrated by the fact that the carbobenzoxy derivative of 8-amino-6-methoxyquinoline was reconverted in reasonably good yield to the parent compound during hydrogenation according to the method previously used. These data would seem to also eliminate (3), failure of hydrogenation to remove the blocking group, from the above list. However, it must be remembered that in the case of UM-122Q the blocking group is attached to a secondary amine while in 8-amino-6-methoxyquinoline the amine in question is primary. No previous use of carbobenzoxychloride as a blocking reagent for secondary amino groups could be found in the literature. However, the carbobenzoxy derivative involving the secondary amine of SN-13,276 was prepared and isolated as an oil which could not be purified. Hydrogenation of this material did not yield anything which could be identified as SN-13,276.

In order to investigate (2), an excess of carbobenzoxychloride was allowed to react with UM-122Q. Although the analytical data are far from satisfactory, a nitrogen analysis indicates that the product might contain two carbobenzoxy groups. A second group, if present, would be expected to involve the phenolic hydroxyl as it appears to be more reactive than the anilino nitrogen. This being the case acetylation of the phenolic hydroxyl could not possibly occur. With this in mind another method for preparing the necessary carbobenzoxy derivative of UM-122Q was considered. A coupling reaction between 8-amino-

6-quinolinol and N-carbobenzoxy-5-isopropylaminopentylchloride (XVII) should produce the desired compound as shown.



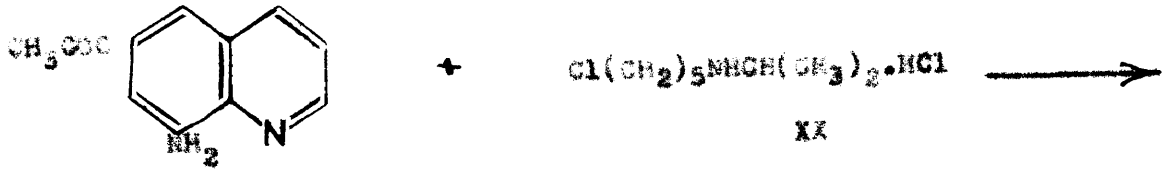
XVII



XVIII

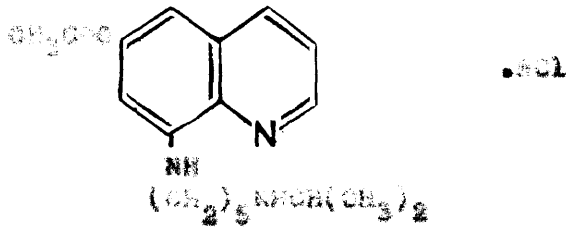
The side chain (XVII) was prepared by the reaction of carbobenzoxychloride with 1-chloro-5-isopropylaminopentane. However, the coupling reaction yielded none of (XVIII) while two-thirds of the side chain was recovered unchanged. Further investigations along these lines were not undertaken as the method showed little promise.

Another method which would be expected to yield 8-(5-isopropylaminoamylamino)-6-quinolyl acetate would involve a coupling reaction between 8-amino-6-quinolyl acetate (XIX) and the appropriate side chain (XX), as shown in the following reaction.

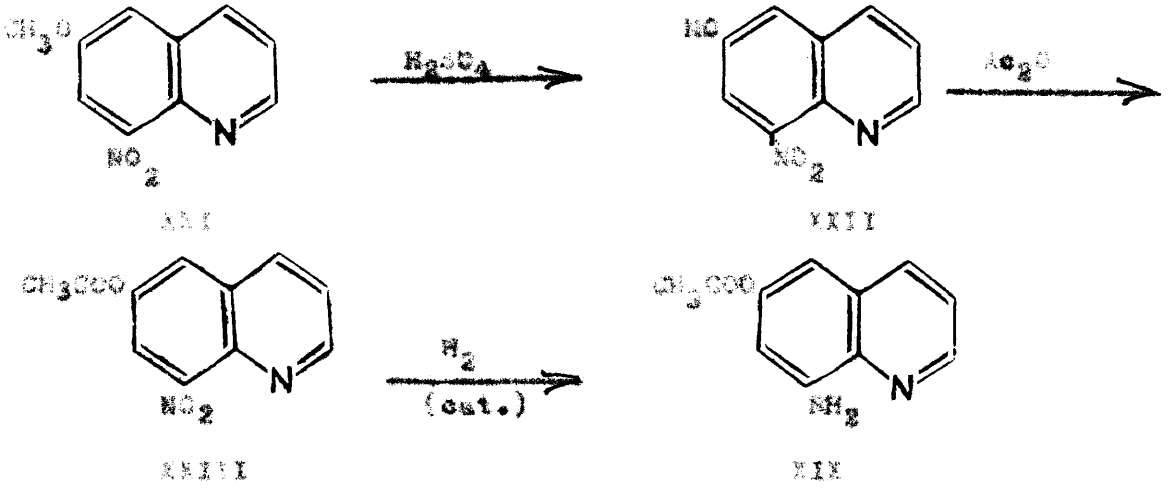


XIX

XX



The quinoline (XIX) required in this reaction might be prepared using one of two methods shown below.



Morgan and Tipson[28] have reported the preparation of 8-nitro-6-quinolinol (XXII) from (XXI), which is commercially available. Heating 8-nitro-6-quinolinol in acetic acid solution with excess acetic anhydride produced 8-nitro-6-quinolyl acetate (XXIII). However, several attempts to reduce the nitro group yielded unstable products which could not be isolated. It was assumed that the discouraging results encountered here were caused by the unstable nature of phenolic esters in neutral solution. In addition migration of the acyl group from oxygen to nitrogen during the reduction is within the realm of possibility.

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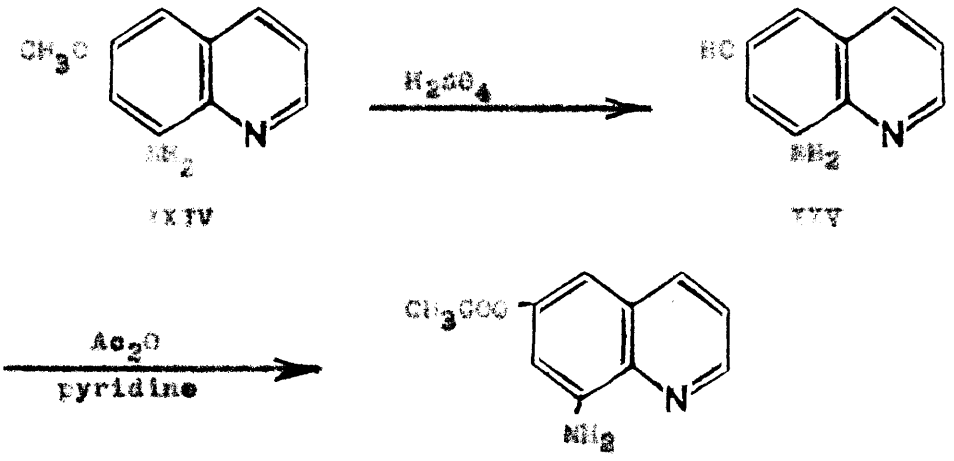
[28]Morgan and Tipson, J. Am. Chem. Soc., 68, 1569 (1946).

As the previously described acyl derivatives of SN-157, are apparently much more stable in acid solution than in neutral or basic media, attempts to reduce the hydrochloride of 8-nitro-6-quinolinol acetate in glacial acetic acid were carried out. However, the results were far from encouraging, and no identifiable product could be isolated.

It was thought that perhaps the benzoate would be more resistant to hydrolysis than the corresponding acetate; a circumstance which might permit its isolation following the hydrogenation reaction. To this end, 8-nitro-6-quinolyl benzoate was prepared, but attempts to reduce this compound did not yield the desired product.

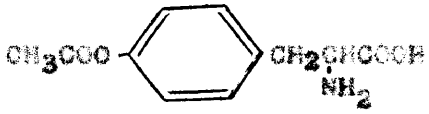
As the above experiments were unsuccessful, attention was shifted to a second method for preparing 8-amino-6-quinolinol acetate. This method is shown in the following series of reactions.



XXIV XXV XXVI

8-Amino-6-quinolinol (XXV) is readily prepared from commercially available 8-amino-6-methoxyquinoline (XXIV) by demethylation with dilute sulfuric acid. However, attempts to prepare 8-amino-6-quinolinol acetate (XXVI)by acetylation with acetic anhydride in pyridine were unsuccessful.

These investigations were again turned toward direct acetylation of UM-122Q. It is known that acetylations of amine salts take place much less readily than do similar reactions involving the free amine. The proton is apparently a rather effective blocking group in this case. Cope and Hancock[29] have reported the successful esterification of several amino alcohols by operating on the amine salts in acid media. These workers also state that other methods for direct esterification yielded the corresponding amide. Another, more striking, example is the O-acetylation (XXVII) of the amino acid tyrosine in strong acid media by Sakami and Toennies.[30]



XXVIII

These workers claim that this represents the first successful attempts to prepare this compound. Of the several trials directed toward the acetylation of UM-122Q in acidic media a few yielded reaction products which could not be purified for characterization. In most of the reactions the salts of UM-122Q were recovered unchanged. Lack of time prevented this portion of the work from being carried to a successful conclusion.

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[29] Cope and Hancock, ibid., 66, 1448, 1453 (1944).

[30] Sakami and Toennies, J. Biol. Chem. 144, 203 (1942).

EXPERIMENTAL

Counter-Current Distribution Analysis of 7-Chloro-4-(4-diethylaminocyclohexylamino) quinoline.- Samples of the free base of cis (m.p. 157.8-159°), trans (m.p. 223-225°) and eutectic mixture (m.p. 147-149°) were carried through a 24 plate distribution according to Craig's[12] method. In the case of the eutectic mixture the free base was obtained from a sample of the diphosphate salt. In all cases the system used consisted of benzene and 2 molar phosphate buffer of appropriate pH. Concentrations of the quinolines were determined in a Beckmann spectrophotometer using light of a wave length of 320mmu. As extinction is proportional to concentration, extinction values were used in place of absolute concentrations. The data obtained in these determinations are tabulated in Tables I, II, and III, while a graphic interpretation of the results is to be found in Figs. 1, 2, and 3.

Proper interepretation of the results shown in Table III and Fig. 3, required a separate determination of the distribution coefficient of both the cis and trans forms in identical systems. To this end the distribution coefficients in benzene vs. 2 molar phosphate buffer of pH 6.60 were determined using a concentration of about 0.1 mg./ml. of the free-base in both cases. It was found that the distribution coefficient of the cis form under these conditions was 1.2, while that of the trans was 0.4. It is obvious that the compound having the higher distribution coefficient migrates more rapidly in a counter-current distribution of a mixture, i.e. will be found to a greater extent in the higher fractions. As the cis form was shown to have the higher distribution coefficient then it is probably the material having

the calculated distribution coefficient of 1.7 shown in Fig. 3. All calculations were done according to methods described by Williamson and Craig.[12e]

7-Chloro-4-(4-cyclohexylaminocyclohexylamino) quinoline (SN-14,115).- A mixture of 30 g. (0.15 mole) of DCQ, 60 g. (0.30 mole) of 4-cyclohexylaminocyclohexylamine,[31] and 14.4 g. (0.15 mole) of phenol was heated to an internal temperature of 165±5° for nine hours in a three-necked flask equipped with a stirrer, condenser and thermometer. The reaction mixture was dissolved in 200 ml. of 50 percent acetic acid. This solution was made strongly alkaline by the addition of sodium hydroxide (200 g.) dissolved in water. The resty mass which separated solidified after a short time. The solid was collected by filtration and then partially dried. Fractional crystallization from acetone and acetone-water mixtures yielded 6 g. of crystalline product melting at 203-206°[32] Anal. Calcd. for $C_{21}H_{32}N_3Cl$: C, 70.25; H, 7.81. Found C, 69.13, 69.42; H, 7.93, 8.13.[33] Another fraction of 20 g. (m.p. 131-146°) was obtained. Anal. Found: C, 70.43, 70.58; H, 7.84, 8.02. The amount of both fractions obtained represents a 47 percent yield.

In another preparation, involving 47.9 g. (0.24 mole) of DCQ and 53 g. (0.27 mole) of side chain, the crude reaction product was distilled

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[31] The diamines used in this and subsequent preparations were kindly supplied by Dr. C. W. Todd, du Pont Experimental Station, Wilmington, Delaware.

[32] Melting points are corrected.

[33] Analyses by Eleanor Gerble, Mary Aldridge and Byron Baer of these laboratories.

TABLE I

Distribution of SN-14,477 (*trans*)

System: Benzene vs. 2 molar phosphate buffer of pH 6.68.
Concentration: 0.25 mg./ml.

Tube no. (r)	Extinction at 320 mmu. (T)	Distribution coeff., calcd. (K)	Theoretical extinction, calcd. (K 0.57)
0	0.038	0.066	0.00
1	.032	.051	.002
2	.035	.22	.010
3	.057	.36	.043
4	.109	.64	.128
5	.278	.60	.293
6	.532	.58	.528
7	.788	.56	.774
8	.932	.57	.934
9	.945	.57	.945
10	.808	.59	.808
11	.608	.62	.587
12	.407	.69	.362
13	.261	.75	.191
14	.154	.83	.086
15	.085	1.00	.035
16	.048	1.37	.011
17	.031	1.57	.003
18	.019	2.66	.000
19	.016	3.50	
20	.014	4.87	
21	.013	6.75	
22	.012	12.5	
23	.013	31.4	
24	.017		
Totals	6.282		5.741

$$\frac{5.741}{6.282} \times 100 = 92 \pm 3\ \%\ \text{homogeniety}$$

TABLE II

Distribution of SN-12,108 (*cis*)

System: Benzene vs. 2 molar phosphate buffer of pH 6.53.
Concentration: 0.26 mg./ml.

Tube no. (r)	Extinction at 320 mmu. (T)	Distribution coeff., calcd. (K)	Theoretical extinction, calcd. (K 0.67)
0	0.044	0.031	0.00
1	.033	.067	.001
2	.026	.156	.004
3	.030	.39	.017
4	.062	.63	.058
5	.156	.69	.156
6	.342	.65	.330
7	.569	.67	.569
8	.815	.67	.809
9	.975	.66	.960
10	.963	.67	.963
11	.817	.67	.821
12	.598	.72	.597
13	.397	.77	.370
14	.241	.84	.195
15	.135	.95	.087
16	.072	1.03	.033
17	.035	1.98	.011
18	.027	2.5	.003
19	.021	3.8	.001
20	.020	5.3	.000
21	.020	7.3	
22	.020	13.2	
23	.023	25.0	
24	.024		
Totals	6.485		5.985

$$\frac{5.985}{6.485} \times 100 = 93 \pm 3\ \%\ \text{homogeneity}$$

TABLE [illegible]

Distribution of SN-12,108-14,477 (mixture)

System: Benzene vs. 2 molar phosphate buffer of pH 6.64.
Concentration: 0.20 mg./ml.[a]

Tube no. (r)	Extinction at 320 mmu. (T)	Distribution coef., calcd. (K)	Theoretical extinction, calcd. (K 0.55)	Theoretical extinction, calcd. (K 1.7)	Theoretical extinction, calcd. (total)
0	0.000				
1	.001	.26	0.000		0.001
2	.003	.55	.003		.003
3	.012	.57	.013		.013
4	.036	.56	.037		.037
5	.081	.55	.081		.081
6	.153	.56	.141	0.000	.141
7	.219	.52	.199	.002	.201
8	.242	.60	.233	.007	.240
9	.257	.69	.228	.021	.249
10	.265	.82	.188	.054	.242
11	.277	1.10	.132	.117	.249
12	.329	1.37	.079	.215	.294
13	.415	1.44	.040	.338	.378
14	.469	1.65	.017	.452	.469
15	.515	1.66	.006	.512	.518
16	.478	1.77	.002	.490	.492
17	.392	1.74	.001	.392	.393
18	.270	1.81	.000	.259	.259
19	.154	1.91		.145	.145
20	.074	1.92		.062	.062
21	.027	2.2		.020	.020
22	.008	8.6		.005	.005
23	.006			.001	.001
24	.023			.000	.000
Totals	4.706		1.400	3.092	4.492

$\frac{1.400}{4.706} \times 100 = 30\ \%$ trans $\qquad \frac{3.092}{4.706} \times 100 = 66\ \%$ cis

[a]Calculated from the amount of salt used.

FIGURE 1

COUNTER-CURRENT DISTRIBUTION
OF SN-14,477

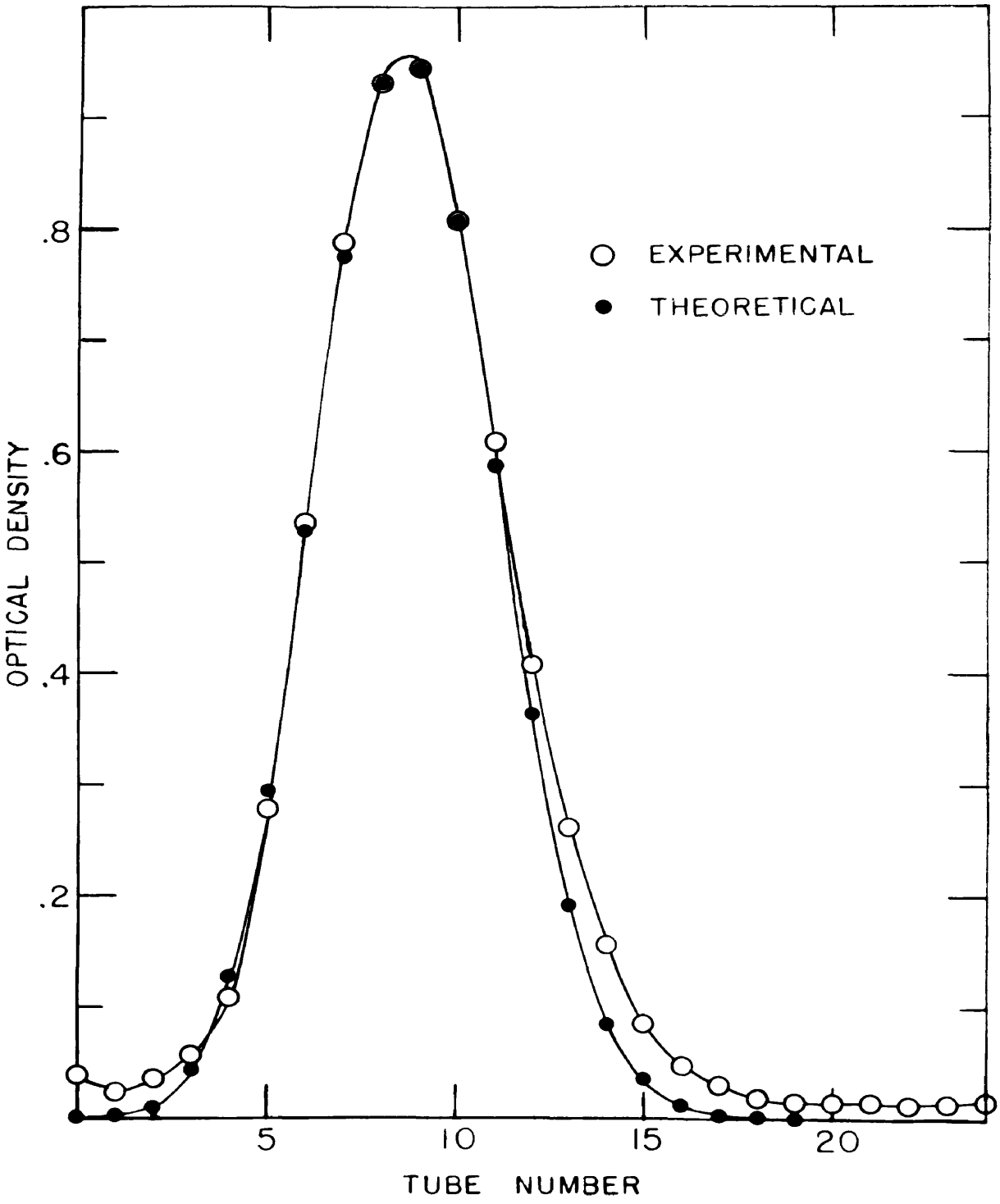


FIGURE 2

COUNTER-CURRENT DISTRIBUTION

OF SN-12,108

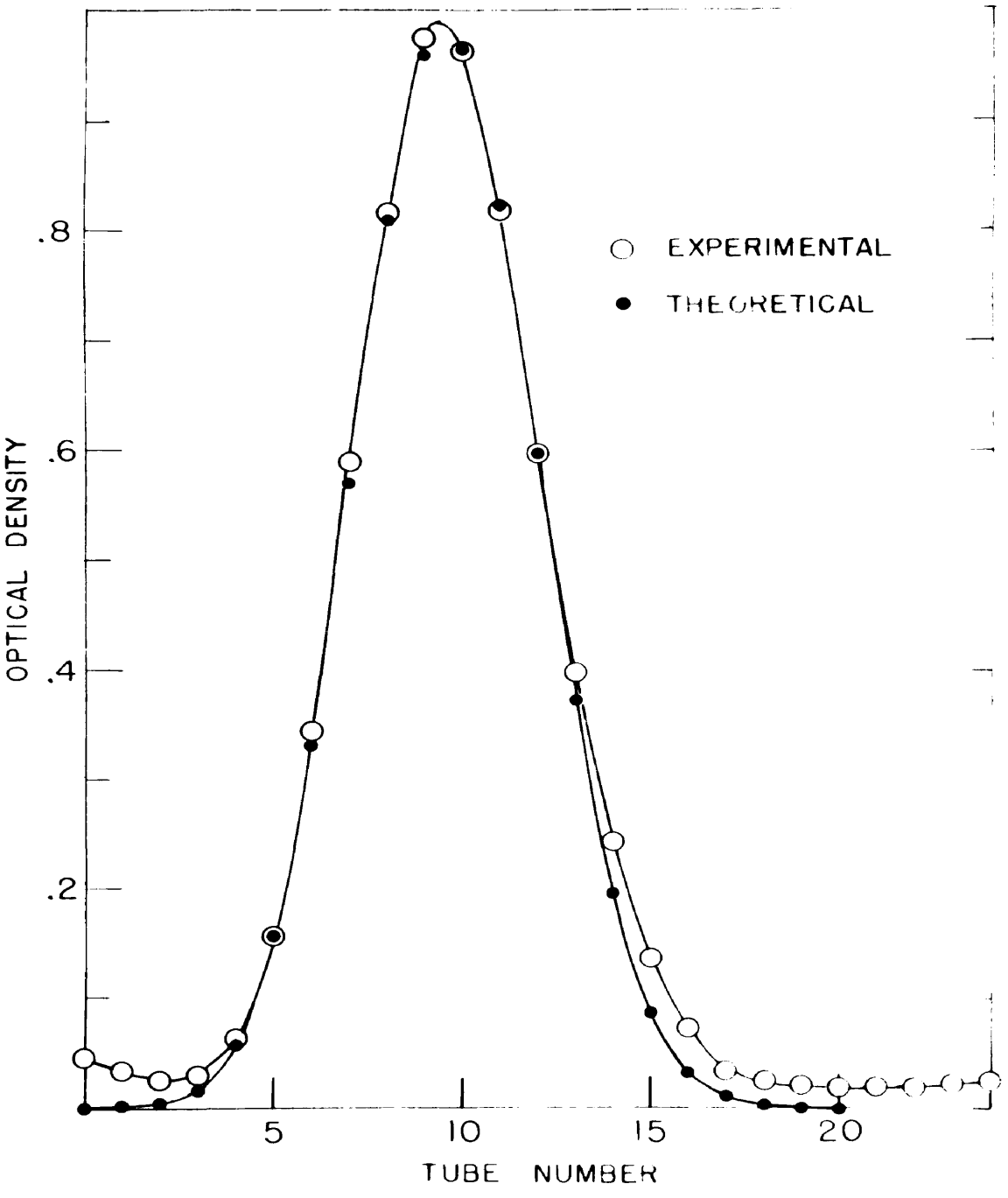
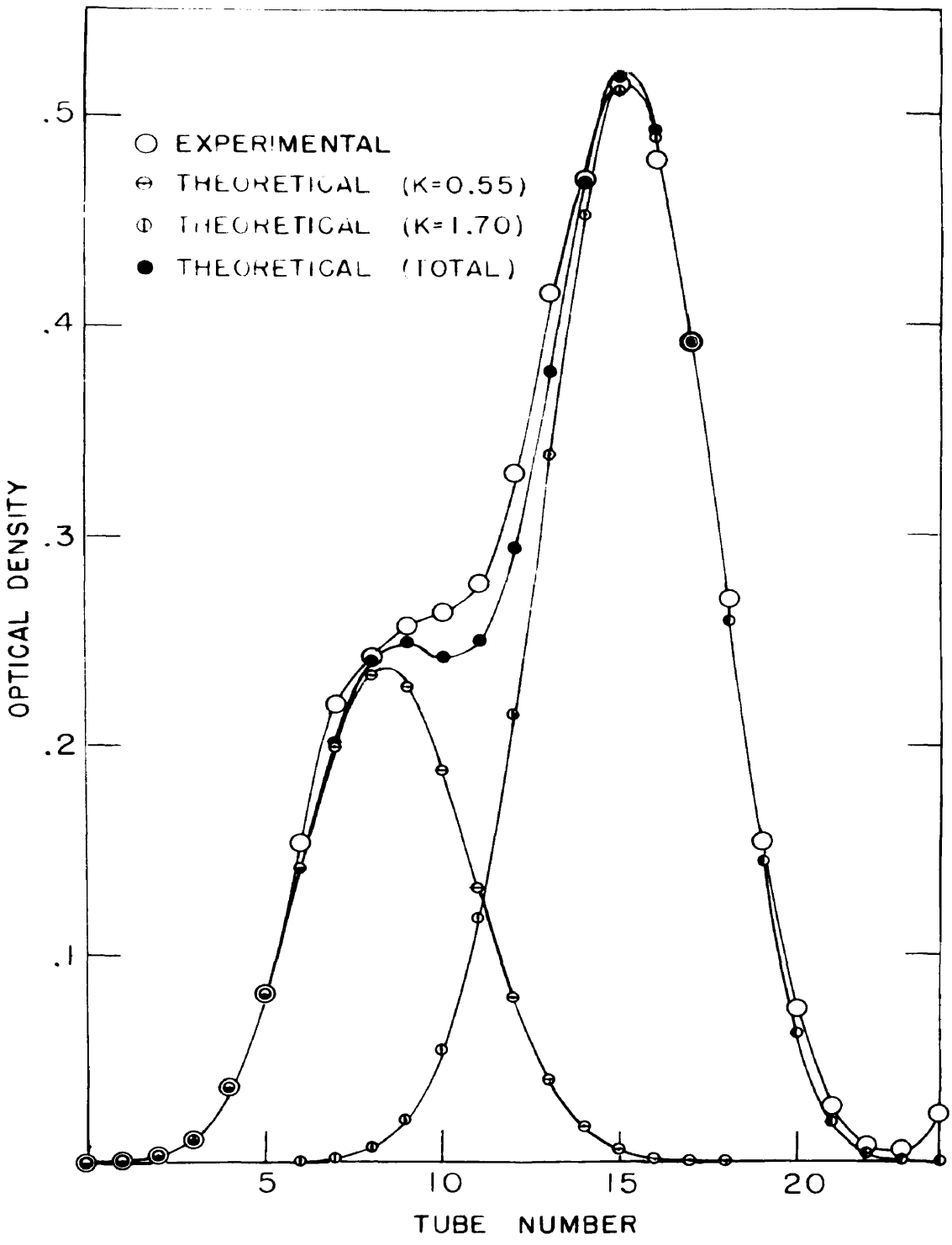


FIGURE 3

COUNTER-CURRENT DISTRIBUTION
OF A MIXTURE OF
SN-12,108 AND SN-14,477



to effect additional purification prior to fractional crystallization. In this manner, 30 g. (60%) of product boiling[34] at 220-230° (2-4-microns, pot 260-270°) was obtained for subsequent crystallization.

7-Chloro-4-(4-ethylaminocyclohexylamino) quinoline.- (SN-15,925) (UM-1234). The coupling of 35 g. (0.175 mole) of DCQ and 49 g. (0.35-mole) of 4-ethylaminocyclohexylamine in 16.8 g. of phenol was carried out essentially as before. The reaction mixture, dissolved in 100 ml. of 60 percent acetic acid was made strongly alkaline by the addition of sodium hydroxide. The aqueous layer was separated from the pasty mass which separated and the organic material was washed several times with water. The crude product was dissolved in alcohol; the alcoholic solution was filtered and finally steam distilled to remove the alcohol and wash out most of the inorganic salts. The residual aqueous layer was decanted from the organic phase which was in turn dissolved in alcohol. The alcoholic solution was filtered, the alcohol removed, and the residue distilled at reduced pressure. About 47 g. (69%) of product boiling at 200-220° (14 microns) was obtained. The product at this stage was combined with 44 g. of material obtained in a similar preparation and fractionally crystallized from acetone and acetone-water mixtures. The higher melting (m.p. 161.5-163°) fraction obtained weighed 22 g. Anal. Calcd. for $C_{17}H_{22}N_3Cl$: C, 67.22; H, 7.30. Found: C, 67.04, 67.32; H, 7.35, 7.28. Another fraction (45 g.) melting at 126-147° was obtained.

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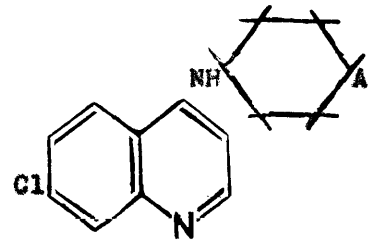
[34] These are not true boiling points but rather the observed distillation temperatures for these compounds in the apparatus used. The observed temperature of distillation varies widely depending on the type of apparatus and the pot temperature.

TABLE IV

4-Aminoquinolines



A	Number		Reaction Conditions		Dist. temp. of base		M. p., trans form, °C.	Yield, %
	UM	SN	temp., °C.	time, hrs.	°C.	microns		
cyclohexylamino	120	14,115	165±5	8.0	220-230	3	203-206	47
ethylamino	123	15,325	165	6.5	200-220	14	161.5-163	89[b]
N-piperidyl	124	15,326	165	6.5	220-225	10	249-250	82[b]
isopropylamino	125	15,327	165	7.5	190-210	25	178-180	82[b]
N-morpholyl	126	15,328	165	5.5	(not distilled)		244-245.5[a]	64
di-n-butylamino	127	15,329	165	6.0	210-220	6	200-201.5	26[c]

[a]In a sealed evacuated tube.

[b]Calculated on the amount of free base before fractional crystallization. All others are calculated on the fractions obtained after crystallization.

[c]Yield calculated on the amount of pure trans modification obtained.

Anal. Found: C, 67.37, 67.77; H, 7.47, 7.46. The combined weight of both fractions represents a 65% yield.

7-Chloro-4(4-(N-piperidyl)cyclohexylamino) quinoline (SN-15,326) (UK-124,).- The reaction mixture from a coupling involving 21.8 g. (0.11 mole) of DCQ and 40 g. (0.22 mole) of 4-(N-piperidyl) cyclohexylamine was dissolved in 150 ml. of alcohol. The alcoholic solution was diluted with water and 20 g. of sodium hydroxide was added. The resulting alkaline mixture was steam distilled to remove the alcohol and excess diamine. The organic portion of the residue was dissolved in alcohol, the solution was filtered and the alcohol removed. The residue was distilled at reduced pressure and 31 g. (82%) of product boiling at 220-225° (10 microns) was obtained. This material was combined with 34 g. of product obtained in a similar reaction and fractionally crystallized from acetone and acetone-water mixtures to obtain 10 g. of the trans form (m.p. 248-250°). Anal. Calcd. for $C_{20}H_{26}N_3Cl$: C, 69.85; H, 7.62. Found: C, 69.53, 69.54; H, 7.99, 7.66. An additional fraction (38 g.) melting at 149-166° was obtained. Anal. Found: C, 70.07, 69.74; H, 7.95, 7.82. The yield of both fractions was 50%.

7-Chloro-4-(4-isopropylaminocyclohexylamino) quinoline (SN-15,327) (UK-125,).- The reaction mixture from a coupling involving 27.5 g. (0.139 mole) of DCQ and 43.4 g. (0.278 mole) of 4-isopropylaminocyclohexylamine in 13.1 g. of phenol was dissolved in 100 ml. of 50 percent acetic acid. Water was added and the solution was made strongly alkaline with sodium hydroxide. The heavy oil which separated solidified completely after about four hours. The solid was removed by filtration and steam distilled as before. When dry this material (48 g.) was combined with 39 g. of the product of a similar coupling (using 28.1 -

g. of DCQ) and distilled at reduced pressure. There was obtained 67 g. (82%) of product boiling at 190-220° (25 microns). Fractional crystallization of the crude product from acetone and acetone-water mixtures yielded a fraction (23 g.) which melted at 178-180°. Anal. Calcd. for $C_{18}H_{24}N_3Cl$: C, 68.00; H, 7.62. Found: C, 67.96, 68.18; H, 7.62, 7.90. A fraction (26 g.) melting at 165-168° was also isolated. Anal. Found: C, 68.15, 68.26; H, 7.46, 7.73. The combined fractions represent a 60% yield.

7-Chloro-4-[4-(N-morpolyl) cyclohexylamino] quinoline (SN-15,328 (UM-126$_4$).- The product from a coupling involving 31.4 g. (0.158 mole) of DCQ and 58.4 g. (0.317 mole) of 4-(N-morpholyl)cyclohexylamine in 14.9 g. of phenol was worked up as in the previous preparation. Following the steam distillation there was obtained 57 g. of crude SN-15,328. This was combined with 36 g. of product from a similar reaction (using 19.4 g. of DCQ) and fractionally crystallized from alcohol. The higher melting form (m.p. 244-245.5°) amounted to 12.5 g. Anal. Calcd. for $C_{19}H_{24}N_3ClO$: C, 66.01; H, 7.00. Found: C, 66.05, 66.14; H, 7.30, 7.14. A second fraction of 44 g. melted at 20[illegible]-240°. Anal. Found: C, 65.90, 66.10; H, 7.08, 7.00. The yield was 64%.

4-(4-di-n-Butylaminocyclohexylamino)-7-chloroquinoline (SN-15,329) (UM-127$_4$).- The reaction mixture from a coupling involving 15.9 g. (0.0802 mole) of DCQ and 36.4 g. (0.161 mole) of 4-di-n-butylaminocyclohexylamine was dissolved in 60 percent acetic acid. Water was added and the solution made strongly alkaline with sodium hydroxide. Following steam distillation, the residual pasty solid was dissolved in alcohol. This solution was filtered, the alcohol was removed and the residue

distilled at reduced pressure. About 31 g. of crude product boiling at 210-220° (6 microns) was collected. Following fractional crystallization from acetone and acetone-water mixtures, 8 g. of the trans form (m.p. 200-201.5°) was obtained. Anal. Calcd. for $C_{23}H_{34}N_3Cl$: C, 71.19; H, 8.83. Found: C, 71.11, 70.90; H, 8.72, 8.93. A second fraction (9 g.) was obtained, but the analysis of this material (C, 71.99, 71.92; H, 8.78, 8.95) indicated that it was impure. Following several recrystallizations there remained 3.9 g. of product melting at 180-197°. Anal. Found: C, 71.85, 71.70; H, 9.07, 8.85. Apparently very little improvement was accomplished by recrystallization.[35] The yield of analytically pure trans form was 26%.

8-(5-Isopropylaminoamylamino)-6-quinolinol (SN-15,324) (UK-1228).- About 20 g. (0.067 mole) of 8-(5-isopropylaminoamylamino)-6-methoxyquinoline (SN-13,276)[36] and 100 g. of redistilled constant boiling hydrobromic acid were heated at 118-120° for three hours while a stream of nitrogen was blown through the reaction mixture. The excess hydrobromic acid was removed at reduced pressure maintaining the temperature of the product at less than 60°. The residue was dissolved in 70 ml. of water and sodium hydroxide solution was added until the product separated as a pasty mass. Eventually this pasty material had solidified completely and was separated by filtration. A portion was dried

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[35]The sample of 4-di-n-butylaminocyclohexylamine used in this preparation was apparently impure. E.E. 119.7, 119.5 (theory 113.2). Private communication from Dr. C. S. Todd, du Pont Experimental Station, Wilmington, Delaware.

[36]Obtained from the Abbott Laboratories, Chicago, Ill.

and found to melt at 151-154.5°. The entire amount was then recrystallized from alcohol and 9 g. of greenish-yellow solid (m.p. 155-157°) was obtained.

A sample of 2 g. of this solid was dissolved in 25 ml. of absolute alcohol, and two molecular equivalents of constant boiling hydriodic acid was added. Following the addition of 46 ml. of ether, a crop of crystalline salt (m.p. 206-209°) was obtained.[37]

The remainder of the base was recrystallized several times from alcohol, but the melting point (155-157°) remained unchanged. Anal. Calcd. for $C_{17}H_{25}N_3O$: C, 71.04; H, 8.77. Found: C, 71.00; H, 8.96. A small portion of this material sublimed rather rapidly at 120-130° (5 microns). The sublimate was a pale yellow solid (m.p. 155-157°). Anal. Found: C, 71.28, 71.16; H, 8.56, 8.75.

In another preparation of UK-122, (using 40 g. of UK-13,276), the excess hydrobromic acid was not removed after the usual heating period. Instead, sodium hydroxide solution was cautiously added until the pH of the solution was about 7.5-8.0. At this point, the precipitated solid was removed by filtration and eventually yielded 19.81 g. of UK-122, (m.p. 155-157°). A second crop of solid (5.4 g.) was recovered from the filtrate. This material melted at 194 - 196° after two recrystallizations from water and one from alcohol.[38] Anal. Calcd. for $C_{17}H_{25}N_3O \cdot HBr$: C, 55.43; H, 7.12. Found: C, 55.25;

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[37]The dihydroiodide of UK-122, melts at 208-208.5°.[15]

[38]The high melting point and almost complete absence of color considered along with the analytical data, indicate the product to be the monohydrobromide of UK-122,.

N, 7.01.

4-(3-Isopropylaminopropylamino)-3-quinolinol Dihydrobromide, Method I.- A solution of 20 g. (0.067 mole) of SN-13,276 and 100 ml. of constant boiling hydrobromic acid was heated, under nitrogen, at 110±2° (internal temperature) for 3.5 hours. Addition of 25 percent sodium hydroxide solution to the cooled reaction was continued until a pH of 7.5 was attained. The precipitated solid was removed by filtration and dried. The dry solid was dissolved in 100 ml. of alcohol and 26.5 g. (0.147 mole) of 48% hydrobromic acid was added. Heating at the boiling point for a short time was necessary to obtain complete solution. Following the addition of 500 ml. of dry ether, there was obtained 27.7 g. (90%) of SN-122, dihydrobromide (m.p. 207-208.5). Anal. Calcd. for $C_{17}H_{25}N_3O \cdot 2HBr$: C, 45.45; H, 6.06. Found: C, 45.71, 45.55; H, 6.18, 5.93.

Method II.-Another demethylation using the same quantities of reactants was carried out as before. Following the heating period, the excess hydrobromic acid was removed at reduced pressure and at an internal temperature not exceeding 60°. The residue was dissolved in 150 ml. of boiling alcohol. While the alcoholic solution was being cooled and stirred, about 750 ml. of dry ether was added. The orange precipitate (26.6 g.) was removed by filtration. The salt was recrystallized from alcohol-ether to yield 26 g. (87%) of product (m.p. 213-215°). Anal. Calcd. for $C_{17}H_{25}N_3O \cdot 2HBr$: C, 45.45; H, 6.06; Br, 35.56. Found: C, 45.41, 45.19; H, 6.06, 6.19; Br, 35.68, 35.59.[39]

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[39]The higher melting point, which did not change during several recrystallizations, is not easily explained. It is thought that this material is an isomorph of the product (m.p. 207-208.5°) which was obtained in previous experiments. The analytical data indicate that this

TABLE V

6-Quinolinols

Product	UM number	Demethylating reagent	M. p., °C. (base)	M. p., °C. (salt)	Yield, %
8-(5-isopropylaminoamylamino)-6-quinolinol (SN-15,324)	122Q	HBr (or H_2SO_4)	155-157	dihydroiodide 206-209 dihydrobromide 207-208.5	60 90[b]
8-(5-diethylaminoamylamino)-6-quinolinol (SN-15,382)	157Q	HBr	130-133[c]	dihydroiodide 194-197 dihydrobromide 221-223	94 77
8-(4-isopropylamino-1-methyl butylamino)-6-quinolinol	173Q	H_2SO_4	121-124[a]	dihydrobromide 215-217	21[b]
8-(5-aminoamylamino)-6-quinolinol	175Q	HBr	---	dihydrobromide 166-169 monohydrate	32[b]
8-(4-diethylamino-1-methylbutyl amino)-6-quinolinol	---	HI	---	dihydroiodide 185.5-188	27[b]
8-amino-6-quinolinol	---	H_2SO_4	174-176[d]	hydrochloride 252-255	24

[a]Anunpurified sample of free base.

[b]Over all yield from the corresponding 6-methoxyquinoline; the remainder are yields of salt from the free base of the corresponding 6-quinolinol.

[c]The free base was obtained in 60 % yield.

[d]The free base was obtained in 80 % yield.

Method III.-A mixture of 20 g. (0.067 mole) of UM-13,276, 22 ml. of conc. sulfuric acid and 40 ml. of water was heated, under nitrogen, at 110±2° for 5.5 hours. A solution of 20% sodium hydroxide was added to the cooled reaction mixture until a pH of 9.5 was attained. The solid which precipitated was removed by filtration and dried. The base was dissolved in 100 ml. of alcohol and 26.5 g. (0.147 mole) of 48% hydrobromic acid. Following the addition of 600 ml. of dry ether, the orange salt of UM-122Q was obtained. Recrystallization yielded 28.5 g. (96%) of product (m.p. 213.5-214.5°).[39]

1-Diethylamino-5-methoxypentane.- A mixture of 154 g. (0.85 mole) of 1-bromo-5-methoxypentane[40] and 124 g. (1.70 moles) of diethylamine was refluxed and stirred for eighteen hours. The reaction mixture was dissolved in 150 ml. of concentrated hydrochloric acid and diluted with 50 ml. of water. The acidic solution was washed with several portions of ether to remove any non-basic products. It was then made strongly alkaline through the addition of sodium hydroxide solution. The organic layer was separated and the aqueous phase was extracted with several portions of ether. The organic layer and combined ether extracts were dried with anhydrous potassium carbonate. The ether was removed and the residue fractionated. The part boiling at 97-99° (22 mm.) (113 g. or 77%) was collected as 1-diethylamino-5-methoxy-

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may be the case. In addition, when this salt was dissolved in water and the solution adjusted to pH 9.5, the free base of UM-122Q (m.p. 155-157°; mixed m.p. 155-157°) was isolated in practically quantitative yield.

[40]John O. Van Hook, Ph.D. thesis, University of Maryland, 1946.

pentane. Anal. Calcd. for $C_{10}H_{23}NO$: neut. equiv. 173. Found: neut. equiv., 174, 176.

1-Bromo-5-diethylaminopentane Hydrobromide.- A solution of 113 g. (0.652 mole) of 1-diethylamino-5-methoxypentane in 600 ml. of 48% hydrobromic acid was heated on the steam cone for three hours. The excess hydrobromic acid was removed at reduced pressure taking care to maintain an internal temperature of less than 80°. The residue, which solidified when cooled to room temperature, was recrystallized from 50 ml. of absolute alcohol, 100 ml. of dry acetone and 1500 ml. of absolute ether. The white crystalline product (178 g.; 90%) melted at 80-82°. Anal. Calcd. for $C_9H_{20}NBr$: Br^-, 26.37. Found: Br^-, 26.18, 26.28 (Volhard).

8-(5-Diethylaminoamylamino)-6-methoxyquinoline (SN-12,904).- A mixture of 178 g. (0.59 mole) of 1-bromo-5-diethylaminopentane hydrobromide, 205 g. (1.18 moles) of 8-amino-6-methoxyquinoline and 150 ml. of water was heated at 80° (temp. of reactants) for twenty hours. The reaction mixture was poured into 150 ml. of water and the pH of the solution adjusted to 5.0. After being warmed to 65° this mixture was extracted with several portions of warm toluene to remove the excess 8-amino-6-methoxyquinoline. The aqueous phase was made strongly alkaline by the addition of sodium hydroxide and the product was extracted with several portions of ether. The ether extracts were combined and dried. The ether was removed and the residue distilled at reduced pressure. That portion (133 g.; 72%) which boiled at 173-176° (75 microns) was collected as SN-12,904. A portion of the base was converted to the oxalate (m.p. 87-89°; lit. m.p. 87-90° and 90-91°).[41]

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[41] Elderfield, et al., J. Am. Chem. Soc., 68,1524 (1946).

8-(5-Diethylaminoamylamino)-6-quinolinol (SN-15,382) (UK-157,).- A solution of 113 g. (0.36 mole) of 8-(5-diethylaminoamylamino)-6-methoxyquinoline in 565 g. of 48% hydrobromic acid was heated, under nitrogen, at 110-115° for two hours. The reaction product was isolated as in the case of UK-122, by the addition of sodium hydroxide solution. The base, after several crystallizations from alcohol, melted at 130-133° (65 g.; 60%). A 4 g. portion of the base distilled very cleanly at 210-220° (30-50 microns) in a molecular distillation apparatus. A sample of the crystallized distillate was twice sublimed to yield a sublimate which melted at 129-132°. Anal. Calcd. for $C_{18}H_{27}N_3O$: C, 71.71; H, 9.03. Found: C, 71.43, 71,65; H, 8.98, 8.72.

8-(5-Diethylaminoamylamino)-6-quinolinol Dihydroiodide.- The salt from 2 g. of the above base was prepared in the usual manner using two molecular equivalents of constant boiling hydriodic acid. Several recrystallizations from alcohol and ether yielded 3.5 g. (94%) of the dihydroiodide of UK-157, (m.p. 194-197°).

8-(5-Diethylaminoamylamino)-6-quinolinol Dihydrobromide.- From 5 g. (0.0166 mole) of the quinolinol and 5.5 g. (0.033 mole) of 48% hydrobromic acid there was obtained in the usual manner 6.5 g. of the crude salt. After several recrystallizations from alcohol-ether, there remained 5.9 g. (77%) of UK-157, dihydrobromide (m.p. 221-223°). Anal. Calcd. for $C_{18}H_{27}N_3O \cdot 2HBr$: C, 46.66; H, 6.31. Found: C, 46.56, 46.34; H, 6.43, 6.63.

8-(5-Aminoamylamino)-6-quinolinol Dihydrobromide (UK-175,).- Using 20 g. (0.076 mole), 8-(5-aminoamylamino)-6-methoxyquinoline (SN-3,851)[42]

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[42]Prepared according to directions described by John A. Carman, Ph.D. thesis, University of Maryland, 1948.

was demethylated in the usual manner. The 23 g. of base obtained was crystallized with extreme difficulty. The crude base was converted directly without further purification to the dihydrobromide salt. The purification of the salt was hindered by the formation of a low melting product.[43] After several recrystallizations 10 g. (32%) of salt remained. This sample melted at 125-128°, but after being dried in the pistol for 24 hours at 100° the melting point had changed to 166-169°. Anal. Calcd. for $C_{14}H_{19}N_3O \cdot 2HBr \cdot H_2O$: C, 39.54; H, 5.45. Found: C, 39.63, 39.71; H, 5.38, 5.74.

8-(4-Isopropylamino-1-methylbutylamino)-6-quinolinol Dihydrobromide (SN-173,).- A solution of 20 g. (0.067 mole) of 8-(4-isopropylamino-1-methylbutylamino)-6-methoxyquinoline (SN-13,274)[44] in 22 ml. of concentrated sulfuric acid and 40 ml. of water was heated at 110±1° for four hours. The reaction mixture was adjusted to pH 9.5 by adding sodium hydroxide solution. The heavy oil which separated did not crystallize. It was dissolved in alcohol and after being refrigerated for three days a crop of solid (7.6 g.) was obtained (m.p. 121-124°). The crude base was converted directly into dihydrobromide in the usual manner. Slow crystallization caused considerable difficulty in the purification of the salt. After several recrystallizations there was obtained 6.3 g. (21%) of the product (m.p. 215-217°).- Anal. Calcd. for $C_{17}H_{25}N_3O \cdot 2HBr$: C, 45.45; H, 6.06. Found: C, 45.44, 45.37; H,

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[43]The melting point of this material varied inconsistantly (from 118 to 133°) and at times the melt partially resolidified. In one recrystallization using absolute alcohol and absolute ether, the product melted at 202-210°.

[44]Supplied by Dr. P.G. Elderfield, Columbia University.

6.12, 6.17.

8-(4-Diethylamino-1-methylbutylamino)-6-quinolinol Dihydroiodide.- The demethylation of 58 g. (0.184 mole) of Plasmochin using 800 ml. of constant boiling hydriodic acid was carried out according to the previously described method for the demethylation of SN-11,191[45]. The crude dihydroiodide of the product (41.g.; m.p. 172-179°) was recrystallized repeatedly from alcohol-ether. There was finally obtained 28 g. (27%) of the purified product (m.p. 185.5-188°). Anal. Calcd. for $C_{18}H_{27}N_3O \cdot 2HI$: C, 38.79; H, 5.25. Found: C, 38.92, 38.92; H, 5.32, 5.34.

8-(5-Diethylaminoamylamino)-6-quinolyl Acetate (SN-15,483) (UN-158).- To 15 ml. of dry pyridine was added 10 g. (0.033 mole) of 8-(5-diethylaminoamylamino)-6-quinolinol and 3.4 g. (0.033 mole) of redistilled acetic anhydride. After standing at room temperature for twenty-four hours in a glass toppered bottle, the solution was poured onto 150 ml. of ice and water. Sodium hydroxide was added until the solution was strongly alkaline and the product was then extracted with four 25 ml. portions of chloroform. The chloroform extracts were combined and dried with anhydrous magnesium sulfate. After filtering, to remove the drying agent, most of the chloroform was removed on the steam bath. The last traces of chloroform and the pyridine were removed at reduced pressure. The residue was distilled from a Hickman pot type molecular still and a fraction (8.1 g.; 71%) distilling at 190-200° (10-12 microns) was collected.

8-(5-Diethylaminoamylamino)-6-quinolyl Acetate Dihydroiodide.-

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[45]Drake, et al., J. Am. Chem. Soc., 68, 1536 (1946).

A 3.45 g. (0.0101 mole) portion of the corresponding quinolyl acetate was dissolved in 10 ml. of alcohol and 4.29 g. (0.0205 mole) of 57% hydriodic acid was added while the mixture was cooled. Crystallization of the salt was effected by adding 100 ml. of ether. The crude product (5.6 g.) melted at 155-156°. After two recrystallizations from alcohol-ether there remained 4.9 g. (81%) of the salt (m.p. 158.5-160.5°).

Anal. Calcd. for $C_{20}H_{29}N_3O_2 \cdot 2HI$: C, 40.08; H, 5.21. Found: C, 39.80, 39.84; H, 5.36, 5.34.

8-(5-Diethylaminoamylamino)-6-quinolyl Acetate Dihydrobromide.- To a solution of 17 g. (0.0495 mole) of the base in 50 ml. of absolute alcohol was added 16.75 g. (0.099 mole) of 48% hydrobromic acid. The precipitate obtained after the addition of 200 ml. of absolute ether weighed 25 g. (m.p. 138-141°). Following four recrystallizations from alcohol-ether, there remained 20 g. (60%) of the purified salt (m.p.140.5-141.5°).

8-(5-Diethylaminoamylamino)-6-quinolyl Benzoate (SN-13,434) (UK-159,4).- In this preparation 10 g. (0.0332 mole) of the corresponding quinolinol in 15 ml. of pyridine was treated with 7.5 g. (0.0332 mole) of benzoic anhydride and the mixture was allowed to stand at room temperature for thirty hours. The product was isolated in essentially the same manner as was UK-156,4. It distilled at 250-260° (10 microns) in the Hickman molecular still. The viscous yellow oil which was collected weighed 8.2 g. (61%).

8-(5-Diethylaminoamylamino)-6-quinolyl Benzoate Dihydroiodide.- The salt from 8.15 g. (0.0201 mole) of the quinolyl benzoate was prepared as before using two molecular equivalents of hydriodic acid. The 12.5 g. of crude salt obtained was recrystallized three times from

alcohol-ether to give 8.68 g. (65%) of the product which melted at 164-166°. Anal. Calcd. for $C_{25}H_{31}N_3O_2 \cdot 2HI$: C, 45.40; H, 5.03. Found C, 45.70, 45.58; H, 5.36, 5.18.

8-(5-Diethylaminoamylamino)-6-quinolyl Benzoate Dihydrobromide.- This salt, prepared in essentially the same manner from 20.7 g. (0.0511 mole) of the base and two equivalents of hydrobromic acid, melted at 125-126° after five recrystallizations from alcohol-ether. The yield was 20 g. (69%). Anal. Calcd. for $C_{25}H_{31}N_3O_2 \cdot 2HBr \cdot \frac{1}{2}H_2O$: C, 51.29; H, 6.03. Found: C, 51.48, 51.57; H, 6.17, 6.14.

8-(5-Diethylaminoamylamino)-6-quinolyl p-Chlorobenzoate (UK-174,).- A mixture of 30 g. (0.096 mole) of 8-(5-diethylaminoamylamino)-6-quinolinol and 29.4 g. (0.096 mole) of p-chlorobenzoic anhydride in 45 ml. of dry pyridine was allowed to stand at room temperature for seven days. At this time only very small amounts of the anhydride remained undissolved. The product was isolated in the usual manner. Distillation from a molecular still at 225-235°(10-20 microns) yielded 31 g. (71%) of an extremely viscous yellow oil.

8-(5-Diethylaminoamylamino)-6-quinolyl p-Chlorobenzoate Dihydrobromide.- The 31 g. (0.0704 mole) of base from above was dissolved in alcohol and treated with 26.3 g. (0.158 mole) of 48% hydrobromic acid. Following the addition of ether there was precipitated 39 g. of salt which melted at 186-188°. After three recrystallizations from alcohol-ether there remained 25 g. of product (m.p. 190.5-192°). Anal. Calcd. for $C_{25}H_{32}N_3O_2Cl \cdot 2HBr + 0.90\%$ moisture: C, 49.44; H, 5.41; moisture, 0.90. Found: C, 49.13, 49.16; H, 5.62, 5.65; moisture, 0.84, 0.95.

6-(p-Carbobenzoxy) amino-8-methoxyquinoline.- A solution of 8.7 g.

(0.05 mole) of 8-amino-6-methoxyquinoline in 50 ml. of absolute ether (alcohol free) was suspended over 50 ml. of 10% sodium hydroxide solution. To this mixture, which was cooled in an ice-bath, 9.4 g. (0.055 mole) of carbobenzoxychloride in toluene[46] was added with stirring. After the addition, which took fifteen minutes, the ice-bath was removed and stirring was continued an additional fifteen minutes at room temperature. The mixture was filtered, and 11 g. of bright yellow crystals were collected. A second crop (4 g.) was recovered from the ether layer. These portions were combined and recrystallized several times from alcohol. There was obtained 11 g. (71%) of well formed, colorless needles which melted at 123-124°. An analytical sample, prepared by washing a part of the above with a large volume of water followed by recrystallization from alcohol, melted at 123-123.5°. Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23. Found: C, 69.60; H, 5.23.

Hydrogenation of 8-(N-Carbobenzoxy)amino-6-methoxyquinoline.- A solution of 8 g. (0.026 mole) of the above on 100 ml. of methanol was warmed and shaken with hydrogen (40 p.s.i.) in the presence of palladium catalyst.[47] After two hours[48] the reaction mixture was filtered to remove the catalyst. The filtrate was concentrated to about 25 ml. on the steam bath, and an excess of constant boiling hydrochloric acid was added. Following the addition of ether, the salt which precipitated was collected. The hydrochloride of 8-amino-6-methoxyquinoline (4.5 g.;

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[46] Org. Syn., Vol. 23, p. 13.

[47] Org. Syn., Coll. Vol. II, p. 568.

[48] There is no pressure drop in this hydrogenation as a mole of carbon dioxide is produced for every mole of hydrogen used.

70%) which was obtained melted at 232-234°.[49]

N-Carbobenzoxy-1-chloro-5-isopropylaminopentane.- To a solution of 1-chloro-5-isopropylaminopentane hydrochloride[15] in 100 ml. of water, was added 100 ml. of 25% sodium hydroxide solution and an excess (30 ml.) of carbobenzoxychloride reagent. During the addition, which took fifteen minutes, the mixture was cooled in an ice-bath and stirred vigorously. The ice-bath was removed while stirring was continued an additional thirty minutes at room temperature. The aqueous layer was separated and the ether layer was washed with 5% hydrochloric acid to remove any basic impurities. The ether solution was dried with anhydrous magnesium sulfate. The ether was removed and the residue was distilled at reduced pressure in the Hickman apparatus. A fraction (15.2 g.; 61%) which distilled at 145-150° (9-12 microns) was collected as the product (n^{27}_D 1.508). Anal. Calcd. for $C_{16}H_{24}NO_2Cl$: C, 64.52; H, 8.12. Found: C, 64.35; H, 7.65.

8-Amino-6-quinolinol.- A solution of 130.5 g. (0.75 mole) of 8-amino-6-methoxyquinoline, 180 ml. of concentrated sulfuric acid and 440 ml. of water was refluxed for twelve hours. Slow cooling of the reaction solution caused the separation of the yellow crystalline sulfate of the product. The sulfate was removed by filtration and, while still wet, was dissolved in 1500 ml. of hot water. The base precipitated after the addition of enough solid sodium bicarbonate to neutralize the sulfuric acid. The red-brown solid changed to a dull green color on standing. The crude quinolinol (103 g.; 86%) melted at 164-167°. The crude product was further purified by recrystallization from alcohol.

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[49]Melting point of an authentic sample of 8-amino-6-methoxyquinoline hydrochloride (233-234.5°).

TABLE VI

8-(5-Diethylaminoamylamino)-6-quinolyl Esters

Ester	UM number	Dist. temp. of base, °C.	(microns)	Yield of base %	M. p., salts, °C.	Yield of salt, %
Acetate(SN-15,433)	158Q	190-200	10-12	71	dihydroiodide 158.5-160.5	82
					dihydrobromide 138-141	80
Benzoate(SN-15,434)	159Q	250-260	10	61	dihydroiodide 164-166	65
					dihydrobromide monohydrate 125-128	69
p-Chlorobenzoate	174Q	225-235[a]	10-20	71	dihydrobromide 190.5-192.0	59

[a]This base was distilled in a molecular still equipped with a magnetic stirring apparatus. Apparently stirring permits distillation to occur at lower temperatures.

It was then dissolved in aqueous alkali, treated with decolorizing carbon, filtered through a carbon mat and finally reprecipitated by adjusting the pH of the solution to 9. A similar operation was carried out with the product dissolved in aqueous acid. Following reprecipitation, the quinolinol was again recrystallized from alcohol to yield 70 g. (58%) of a dark green solid. Anal. Calcd. for $C_9H_8N_2O$: C, 67.06; H, 5.00. Found: C, 66.91, 66.83; H, 5.20, 5.12.

8-Amino-6-quinolinol Hydrochloride.- The salt from 5 g. (0.031 mole) of the corresponding quinolinol was prepared in excess aqueous hydrochloric acid and precipitated with alcohol. Recrystallization from hot water-alcohol mixtures eventually yielded 2.4 g. (39%) of the hydrochloride salt (m.p. 252-255°).

Attempted Coupling of 8-Amino-6-quinolinol with N-Carbobenzoxy-1-chloro-5-isopropylaminopentane.- A mixture of 16 g. (0.10 mole) of 8-amino-6-quinolinol and 15 g. of N-carbobenzoxy-1-chloro-5-isopropylaminopentane in 25 ml. of cellosolve[50] was heated at 100° for twenty hours. The reaction mixture was poured into water and neutralized with sodium hydroxide solution (pH 8.5-9.0). This solution was extracted with several portions of chloroform, and the extracts were combined and dried. The chloroform was removed and the residue distilled in the molecular distillation apparatus. The only fraction (10 g.) which could be obtained distilled at 130-150°(5-15 microns) (n_D^{25} 1.503), and is apparently unreacted side chain. No other product could be isolated from this reaction.

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[50]Cellosolve was used as the solvent because the reactants in this case are insoluble in water, the usual coupling solvent.

8-Nitro-6-quinolyl Acetate.- A mixture of 55 g. (0.31 mole) of 8-nitro-6-quinolinol (25), 60 ml. of acetic anhydride and 60 ml. of acetic acid was refluxed for ten hours. The reaction mixture was poured onto ice and water, and the solid which precipitated was removed by filtration. The product was twice recrystallized from alcohol to obtain 26.8 g. (37%) of tan crystals (m.p. 107-111°). A portion recrystallized several more times from alcohol melted at 110-112°. Anal. Calcd. for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47. Found: C, 57.22; H, 3.35.

8-Nitro-6-quinolyl Benzoate.- A mixture of 5 g. (0.026 mole) of 8-nitro-6-quinolinol and 10 g. (0.043 mole) of benzoic anhydride was heated at 120-140° for three hours. The melt which was now homogeneous was poured onto ice and water. The pasty mass which separated did not crystallize, so the water layer was decanted and the organic phase was dissolved in chloroform. The chloroform solution was dried and most of the solvent distilled. Upon the addition of petroleum ether (b.p. 30-60°), a solid precipitated which after recrystallization from alcohol weighed 3.1 g. (37%) (m.p. 131-132°). Recrystallization of the product did not change the melting point. Anal. Calcd. for $C_{16}H_{10}N_2O_4$: C, 65.30; H, 3.43. Found: C, 64.98; H, 3.48.

TABLE VII

Testing Data[a]

Compound		Test	Evaluation
UM	SN		
122Q	15,324	A-1	Q 12
			Q 32
		A-2	inactive at mtd.
		A-2a	inactive at mtd.
		D-1	Q 4
		1-A	Q 12
			Q 20
		2-U	1/16 to 1/8 x SN-971
123Q	15,325	A-1	Q 16
		A-2	inactive at ftd.
		A-2a	inactive at ftd.
		D-1	Q 8
		1-A	Q 15
124Q	15,326	A-1	Q 8
		A-2	inactive at ftd.
		A-2a	inactive at ftd.
		D-1	Q 4
		1-A	Q 10
125Q	15,327	A-1	Q 16
		A-2	inactive at ftd.
		A-2a	inactive at ftd.
		D-1	Q 8
		1-A	Q 20
126Q	15,328	A-1	Q 4
		1-A	Q 12
127Q	15,329	A-1	Q 4
		A-2	inactive at ftd.
		A-2a	inactive at ftd.
		1-A	Q 12

[a]Description of the tests and meaning of the evaluation is described in the monograph.[2] This data was obtained in private communications from Dr. E. K. Marshall, Johns Hopkins University, Dr. R. Coatney, National Institute of Health, and Dr. Richardson, Squibb Institute for Medical Research.

TABLE VII (cont.)

Compound		Test	Evaluation
UM	SN		
157Q	15,382	P. lophurae (ducks)	Q 5
		P. lophurae (chicks)	Q 70
		P. cathemerium (ducks)	Q 15
		A-1	Q 16
		1-A	Q 2.5
158Q	15,433	A-1	Q 8
		1-A	Q 30
159Q	15,434	A-1	Q 8
		1-A	Q 20

TABLE VIII

Clinical Testing Results on SN-15,324[f]

Prophylactic Tests

Total dose[a] (g.)	Mean plasma conc. during treatment	Schedule of Admin. (days)	Observed period neg. cases (days)	Treated Patients: Patent infec./ indiv. exposed	Treated Patients: Prepatent period (positive cases) fever/parasite	Controls: Patent infec./ indiv. exposed	Controls: Prepatent period (positive cases) fever/parasite
0.96	---,---	1-1-6[b]	144	1/2	16/16,__	3/3	12/13,20/19,19/17

Therapeutic Tests[e]

Period of admin. (days)	Nature of attack	Total dose (g.)	Mean plasma conc. during treatment	No. subjects relapsed/ no. treated: Total	A	B	Days from end of treatment to relapse fever/parasite	Days after treatment in negative cases
14	P^c, R_2, R_2, R_2^d	0.42	gamma/liter --,--,--,--	4/4	4/4	0/0	13/9,16/14,14/10,16/12	--,--,--,--
14	R_2, R_2, R_2, R_2, R_2	0.84	gamma/liter --,--,--,--,--	4/5	4/5	0/0	73/73,__,10/14,__,16/12	--,--,--,--,--
14	R ,R ,F,F,F,	1.68	gamma/liter --,--,--,--,--	5/5	5/5	0/0	43/40,17/20,11/11,8/8,44/43	--,--,--,--,--

Toxicity Tests[e]

Daily dose (mg.)	Total dose (g.)	Duration (days)	Methgb. formation (% of total hgb.)	Symptoms, unless otherwise specified resemble those of the pamaquine regime with a similar methemoglobin index	Approximate pamaquine daily dosage (mg.) (Q = quinine)
30	0.42	14	2.4		15 Q
60	0.84	14	3.4		15 Q
120	1.68	14	2.8	Frequent moderate abdominal pain	45 Q

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[a]All drug doses are reported as free base. [b]Indicates the drug was administered the day before inoculation, the day of inoculation and for six subsequent days. [c]Indicates a primary attack. [d]Indicates a second relapse. [e]Drug administered along with a total of 23 g. of quinine. [f]Taken from N.I.H. Malaria Report No. 30, U.S.P.H.S. Antimalarial Grant No. 198. Responsible investigators, Drs. Alving and Coggeshall.

ABSTRACT

Edward Galton, Ph. D., 1948 (B.S. University of Maryland)
Title of Thesis: Synthetic Antimalarials
Thesis directed by Professor Nathan L. Drake
Major: Organic Chemistry, Department of Chemistry
Minors: Physical Chemistry, Inorganic Chemistry
Pages in thesis 54. Words in abstract 341.

Wartime researches in the field of antimalarial drugs revealed many 4- and 8-aminoquinolines of potential interest. Following the customary procedure in a search of this type, a host of structurally related compounds were prepared in the hope of bringing to light more active and less toxic preparations which might be useful in the control and cure of malaria.

A series of six 7-chloroquinolines, containing variously substituted cyclohexylamine side chains in the 4- position, were prepared as a continuation of the series headed by 7-chloro-4-(4-diethylaminocyclohexylamino) quinoline, a drug possessing rather favorable suppressive activity. The six new compounds were prepared in a coupling reaction of 4.7-dichloroquinoline with the appropriate diamine. The products obtained were 7-chloro-4-(4-cyclohexylaminocyclohexylamino)quinoline, 7-chloro-4-(4-ethylaminocyclohexylamino)quinoline, 7-chloro-4-(4-isopropylaminocyclohexylamino)quinoline, 7-chloro-4-(4(N-piperidyl)cyclohexylamino) quinoline, 7-chloro-4-(4-(N-morpholyl)cyclohexylamino)quinoline and 4-(4-di-n-butylaminocyclohexylamino)-7-chloroquinoline.

7-Chloro-4-(4-diethylaminocyclohexylamino)quinoline had been previously separated into three fractions by a tedious fractional crystallization. The present work describes a counter-current distribution analysis of these three fractions. It was determined that the fractions which melted at 157.8-159° and 223-225° are within a few percent the

pure individual cis and trans isomers respectively. That fraction which melted at 147-149° was shown to be a probable eutectic mixture of both geometric isomers in the approximate ratio of 30 percent trans and 66 percent cis.

The present investigations into the 8-aminoquinolines were concerned with the substituted 8-amino-6-quinolinols and their esters. The previously reported low toxicity of the 6-quinolinols prompted the preparation of five new compounds in this series. These quinolinols were prepared by the demethylation of the corresponding 6-methoxyquinolines by heating in acid media. The compounds prepared were as follows: 8-(5-isopropylaminoamylamino)-6-quinolinol and its dihydrobromide, 8-(5-diethylaminoamylamino)-6-quinolinol and its dihydroiodide and dihydrobromide, 8-(4-isopropylamino-1-methylbutylamino-6-quinolinol dihydrobromide, 8-(4-aminoamylamino)-6-quinolinol dihydrobromide.

In the hope of obtaining higher activity while retaining low toxicity, three 6-quinolyl esters were prepared. The acetate, benzoate, and p-chlorobenzoate of 8-(5-diethylaminoamylamino)-6-quinolinol were obtained by acylation of the quinolinol in pyridine solution using the appropriate acid anhydride.

In the course of unsuccessful attempts to prepare 8-(5-isopropylaminoamylamino)-6-quinolyl esters, several new intermediates were obtained. These compounds include: 8-amino-6-quinolinol and its hydrochloride, 8-nitro-6-quinolyl acetate, 8-nitro-6-quinolyl benzoate, 1-(N-carbobenzoxy)isopropylamino-5-chloropentane and 8-(N-carbobenzoxy) amino-6-methoxyquinoline.

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