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Fluorine and sulfur quinoline derivatives as antimalarial agents

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FLUORINE AND SULFUR QUINOLINE DERIVATIVES AS ANTIMALARIAL AGENTS

by

Leo Loveland Tolman

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

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In Charge of Major Work

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Iowa State College

1945

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I. INTRODUCTION

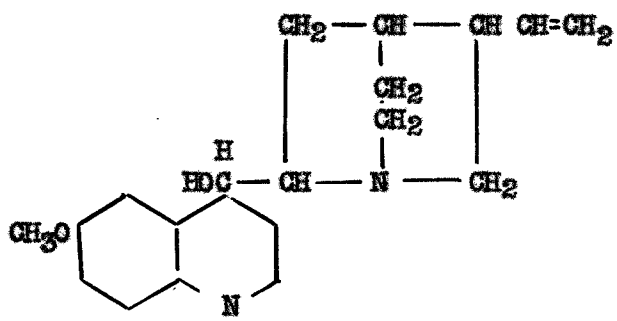
In this nation the application of synthetic organic compounds to the treatment of malaria has greatly increased in the last three years. The interest in synthetic antimalarials has accelerated since the war in the Pacific has virtually eliminated the supply of quinine and many American troops are stationed in areas where malaria is a very serious problem. The threat of malaria will continue after the war since the infected service men will carry the disease to the various sections of the United States that have previously been unaffected by malaria. The anopheline mosquitoes are plentiful in the United States, but most of the mosquitoes are not infected with the malarial parasite since the cases of human malaria, especially in the northern states, have been so scattered.

The three most important malarial drugs at the present time are quinine, plasmoquin, and atebrin. All of these drugs are quinoline derivatives and, although they represent only an approach to the "ideal antimalarial", these agents are very useful in the treatment of malaria. The object of this investigation has been the synthesis of compounds rather closely related to the known antimalarials, in the hope of developing a similar compound which might be more desirable as an agent against malaria. The introduction of sulfur or fluorine atoms into quinoline derivatives has been the general approach in the modification of these known quinoline antimalarials.

II. HISTORICAL

1. General

For over three hundred years quinine (I) has been used in the treatment of malaria. At first the cinchona bark, which contains



(I)

quinine and other alkaloids, was used in the form of a powder. The first real advance in the treatment of malaria occurred in 1820 when quinine was extracted from the bark and used in the pure state. In 1908, Rabe proposed the structure of quinine which is accepted today, and in 1931 he synthesized dihydroquinine.[1] Recently his work was verified by Woodward and Doering,[2] who completed the total synthesis of quinine. This synthesis is probably of no commercial value at the present time since only a very small amount of material has been produced by the laboratory method which involves many steps.

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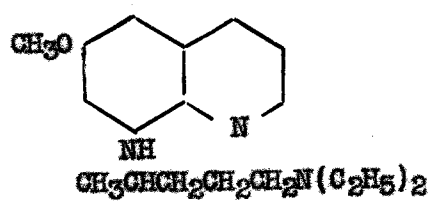
1. Rabe and co-workers, Ber., 64B, 2487 (1931).

2. Woodward and Doering, J. Am. Chem. Soc., 67, 860 (1945).

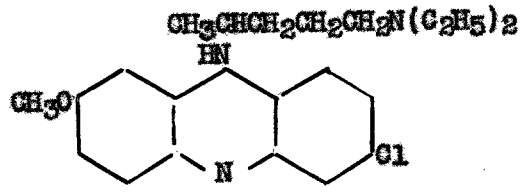
In 1891, Guttman and Ehrlich[3] demonstrated that methylene blue exhibited some antimalarial activity, and later other compounds rather closely related to methylene blue were shown to be of therapeutic value in the treatment of malaria. After years of research, terminated by an extensive systematic program of I. G. Farbenindustrie, plasmoquin (II) was developed in 1924.[4] Plasmoquin is one of the most effective agents



(II)

known in the treatment of avian malaria. Although this compound is very effective in combating avian malaria, its use in the treatment of human malaria is very limited as the therapeutic dose often approaches the toxic dose.

In 1930[5] atebrin (III) was introduced as an antimalarial drug which later proved to be very effective in the treatment of human malaria, and at the present time this compound is the most important synthetic antimalarial. In the current war atebrin has been used almost exclusively.



(III)

3. Guttman and Ehrlich, Berlin. klin. Wochschr., 28, 593 (1891) [Chem. Zentr., I, 221 (1892)].

4. Schuleman et al., Ger. Patent 486,079 (1924) [C. A., 24, 1937 (1930)].

5. (a) Mietzsch and Mauss, Klin. Wochschr., 12, 1276 (1933); (b) U. S. Patent 2,077,249 (1937) [C. A., 31, 4060 (1937)].

Since the introduction of plasmoquin and atebrin, the interest in synthetic antimalarials in this country has increased considerably. In recent years thousands of compounds have been tested under the auspices of the United States government in the hope of finding an antimalarial agent more effective than atebrin or quinine. This investigation represents a part of the government program.

The structures of these three most important drugs are rather closely related. All compounds are 6-methoxyquinoline derivatives and each contains a basic side-chain. In atebrin a chlorobenzo group is fused to the 6-methoxyquinoline nucleus. Atebrin might also be considered as a 7-chloroquinoline derivative and this nucleus has shown antimalarial properties comparable to that of 6-methoxyquinoline nucleus. Plasmoquin and atebrin contain the same side-chains, but the dialkylamino-alkylamino group is attached to the quinoline nucleus in different positions. The bicyclic basic side-chain in quinine is located in a position comparable to that occupied by the side-chain of atebrin; however, the former contains a secondary carbinol group.

In the search for the ideal drug, the prophylactic as well as the therapeutic properties are of extreme importance. One of the serious limitations of both quinine and atebrin as agents against malaria is the absence of prophylactic action. These drugs now used in the treatment of malaria only suppress the action of the malarial parasite; neither complete cure nor preventive action against infection is accomplished by these compounds.

2. Aminosulfides

Methylene blue[3] and very closely related derivatives were some of the first compounds found to have antimalarial activity, but no other phenothiazine derivatives have demonstrated any significant activity.[6] Other heterocyclic sulfur compounds containing the sulfur atom as a sulfide have not shown much promise as antimalarials, but this statement is based on the testing of only a relatively few derivatives. Further testing of heterocyclic sulfide compounds may prove more fruitful.

The pharmacological tests of several compounds containing sulfur with a valence of six have been rather encouraging. For example, sulfanilamide and many of its derivatives[7] have shown definite activity, but these compounds have not shown outstanding antimalarial properties. Some sulfones have been reported as active, especially diphenyl sulfone derivatives.[7]

This investigation has to do primarily with aliphatic side-chains containing a tertiary amino group and a sulfide linkage. At the time this investigation was begun in this laboratory, only two important compounds of this type had been prepared as antimalarials. The first compound was 8-[β-(β'-diethylaminoethylmercapto)-ethylamino]-6-methoxyquinoline[8] (IV), and the second compound was the corresponding 5,6-dimethoxy derivative[9]. Unfortunately the physiological tests on these

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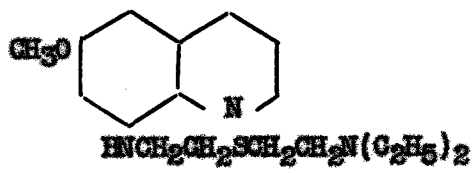
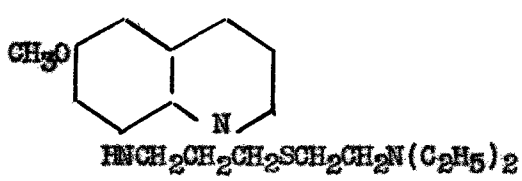
6. Shirley, D. A., Doctoral Dissertation, Iowa State College (1943).
7. Marshall, J. Pharmacol., 75, 89 (1942).
8. (a) Brit. Patent 286,087 (1926) [C. A., 23, 241 (1929)]; (b) Ger. Patent 486,079; 486,771; 488,890; 488,892; 488,945 (1924) [C. A., 24, 2242 (1930)]; (c) Brit. Patent 267,169 (1927); (d) U. S. Patent 1,747,531 (1930)
9. (a) Ger. Patent 536,446 (1930) [C. A., 26, 1067 (1932)]; (b) Brit. Patent 354,352 (1930) [C. A., 26, 5312 (1932)]; (c) U. S. Patent 1,938,047 (1933).



(IV)

compounds are not available. In this laboratory, Gilman and Woods[10] first prepared 8-[γ-(β-diethylaminoethylmercapto)-propylamino] - 6-methoxyquinoline (V) and other derivatives in which the terminal



(V)

diethylamino group was replaced by the piperidino, morpholino, and thiomorpholino groups. Preliminary tests on these sulfide derivatives were very encouraging; therefore, several closely related types were prepared for physiological testing.

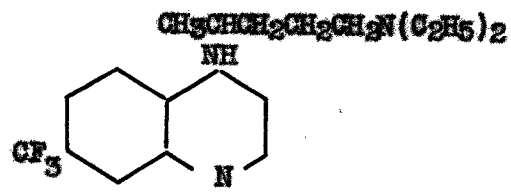
3. Trifluoromethyl Derivatives

Certain aromatic halogen atoms appear to contribute to antimalarial activity as demonstrated by the 6-chloroacridine and 7-chloroquinoline derivatives. In these two groups of compounds the elimination of the chlorine atom from the nucleus, either greatly reduces or completely destroys the activity.

When this investigation was started only a few physiological tests on trifluoromethyl compounds were available. Some simple trifluoromethyl

10. Gilman and Woods, J. Am. Chem. Soc., 67, 000 (1945).

derivatives were prepared in this laboratory, and the preliminary tests were very encouraging. For example, m-trifluoromethylphenol was reported to have some antimalarial activity. Several other rather simple derivatives prepared from m-trifluoromethylaniline were reported inactive. Since most of the physiological tests available were those on rather simple trifluoromethyl derivatives, some quinoline compounds were prepared in the hope that the more complex types would be active. Gilman and Blume[11] first carried out the Skraup synthesis with m-trifluoromethylaniline to obtain primarily 7-trifluoromethylquinoline along with a small percentage of the 5-derivative. The tests on these quinoline compounds were negative, but since the typical basic side-chain was absent from these derivatives, the lack of activity was not particularly discouraging. Recently Andersag and co-workers[12] prepared 4-(δ-diethylamino-α-methylbutylamino)-7-trifluoromethylquinoline (VI), but no



(VI)

physiological tests are available.

4. Miscellaneous Antimalarials

During the course of this investigation, several miscellaneous compounds were prepared in order that they might be tested for antimalarial properties. These compounds have been divided into two

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11. Gilman and Blume, J. Am. Chem. Soc., 65, 2467 (1943).

12. Ger. Patent 683,692 (1939) [C. A., 36, 4973 (1942)].

groups: arsine derivatives and miscellaneous amines.

Arsine Derivatives

Arsenic compounds have been used extensively in the treatment of protozoan diseases such as syphilis; therefore, some antimalarial activity from these compounds would be expected. The arsenic compounds used in the treatment of these diseases are generally arseno compounds, arsonic acids, and arsine oxides. The well known salvarsan or "606" prepared and tested by Ehrlich was an arseno derivative. These compounds are all relatively toxic, but they are administered in quantities which can be tolerated and yet are effective in combating disease. In general, the arsenicals used in treating syphilis also have some therapeutic value in malaria.

The compounds prepared in this investigation were all derivatives of arsine. Prior to this investigation, no report on the antimalarial activity of arsine compounds was available.

Miscellaneous Amines

In planning the preparation of possible antimalarial agents there are really two objectives. The first is the preparation of a compound to be used in combating malaria, and the second is the preparation of a compound which might aid in the correlation of chemical constitution and physiological activity. The vast number of compounds tested for therapeutic activity in malaria has led to the formulation of many generalizations and predictions concerning chemical structure and activity.

Spatz[13] has prepared a rather comprehensive review of chemical constitution and antimalarial action.

In general the exact relationships that exist between antimalarial activity and chemical structure are too complex to be solved at the present time; therefore, a somewhat random preparation of possible drugs has a definite value in antimalarial research. These preparations need not be entirely undirected, as there are certain very broad generalizations which appear to be valid. For example, an aliphatic basic side-chain greatly enhances the activity of some compounds, but this group is not necessary to produce activity. Different basic side-chains have varying effects on the activity of the compound. One interesting basic group which has shown promise is the 2,5-dimethyl-1-pyrryl group. Changes in the terminal basic group of the aliphatic side-chain changes the activity, but the diethylamino group appears to be one of the most effective terminal groups.

Several aromatic nuclei are represented in the group of active antimalarial compounds. The quinoline ring undoubtedly has shown more promise than any other nucleus, but all quinoline compounds do not have antimalarial activity while many other active compounds do not contain the quinoline nucleus. Certain groups such as methoxy, chloro, hydroxy and others attached to any one aromatic ring often enhances the physiological action, but these groups usually are not necessary for antimalarial activity.

These very broad generalizations have initiated the preparation of the miscellaneous amines prepared in this investigation.

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13. Spatz, S. M., Doctoral Dissertation, Iowa State College (1941).

III. EXPERIMENTAL

γ-Hydroxypropyl Mercaptan. This mercaptan was prepared from γ-chloropropanol and aqueous sodium hydrosulfide according to the method described by Rojahn and Lemme.[14] The yields on several preparations varied from 40-60 per cent of the theoretical amount of mercaptan boiling at 87-90°/16 mm.

β-Diethylaminoethyl Chloride. This chloride was prepared in rather large quantities by a modified procedure of the method described by Gough and King.[15] To 1400 g. (13.0 moles) of thionyl chloride in 1 l. of chloroform, 1050 g. (9.0 moles) of β-diethylaminoethanol in 350 ml. of chloroform was added dropwise with vigorous stirring at 0°. After the addition was complete, most of the chloroform and excess thionyl chloride was removed by distillation at reduced pressure from a water bath. As soon as the material began to crystallize, 50 ml. of ethanol was carefully added to destroy the excess thionyl chloride. After distilling more of the volatile material, more ethanol was added. This addition of the ethanol was continued until the thionyl chloride was completely destroyed. Ethyl acetate was added to the crystalline mass until the mixture was fluid enough to filter. The precipitate was washed well with ethyl acetate and dried in the air to give 1270 g. (83%) of material melting at 206-208°. This material was used without further purification, but the melting point of the pure compound is 210-211°.

This hydrochloride was converted to the free base and distilled by the following procedure. To an ice-cold mixture of 300 g. (1.76 moles)

14. Rojahn and Lemme, Arch. Pharm., 263, 612 (1925).

15. Gough and King, J. Chem. Soc., 2437 (1928).

of crude β-diethylaminoethyl chloride hydrochloride and 300 ml. of ether in a 1 l. Erlenmeyer flask was slowly added 250 ml. of ice-cold 35 per cent sodium hydroxide with swirling. The ether was separated and the aqueous layer was extracted with two 200 ml. portions of ether. The ether extracts were combined and dried over anhydrous sodium sulfate. The ether was removed by distillation on a steam bath and the residue was distilled at reduced pressure. The yield was 180 g. (76%) of colorless liquid boiling at 52-55°/21 mm. This material can be stored in an ice-box for at least three or four days.

β-Diethylaminoethyl γ-Hydroxypropyl Sulfide. To 300 ml. of absolute ethanol containing 23 g. (1.0 g. atom) of sodium was added 92 g. (1.0 mole) of γ-hydroxypropyl mercaptan.[14] To this solution 136 g. (1.0 mole) of β-diethylaminoethyl chloride[15] was added dropwise at the reflux temperature. After the addition the mixture was refluxed one-half hour, and then most of the ethanol was removed at reduced pressure. The residue was dissolved in a mixture of ether and water, and the ether layer was separated. This ether extract was dried over anhydrous sodium sulfate, and then distilled to give 143 g. (75%) of product boiling at 105-106°/0.1 mm. Previously Gilman and Woods[10] had prepared this sulfide from β-diethylaminoethyl mercaptan and γ-chloropropanol. These workers also converted the carbinol to the corresponding chloride as described below.

β-Diethylaminoethyl γ-Chloropropyl Sulfide. One-hundred and ten grams (0.58 mole) of β-diethylaminoethyl γ-hydroxypropyl sulfide in 100 ml. of chloroform was added dropwise to a solution of 137 g. (1.15 moles) of purified thionyl chloride in 200 ml. of chloroform. This addition was carried out at 0°, and the time required was one hour. After the addition was complete, the solution was refluxed for one hour,

and then the solvent was removed by distillation at reduced pressure from a steam bath. The residue was treated with ethanol twice to remove the excess thionyl chloride. After removing the volatile material, the residue was cooled in ice and neutralized with a dilute sodium hydroxide solution. The oily product was extracted with ether and dried over anhydrous sodium sulfate. The ether solution was filtered to remove some suspended black material and the drying agent. The product was distilled at reduced pressure to give 87 g. (72%) of a colorless liquid boiling at 92-93°/0.1 mm.

γ-Diethylaminopropyl γ-Hydroxypropyl Sulfide. By the method used to prepare β-diethylaminoethyl γ-hydroxypropyl sulfide (p. 11), this sulfide was prepared from 58 g. (0.63 mole) of γ-hydroxypropyl mercaptan, 14.5 g. (0.63 g. atom) of sodium and 94 g. (0.63 mole) of γ-diethylaminopropyl chloride[16] in 300 ml. of ethanol. The yield was 89 g. (69%) of colorless material boiling at 126-129°/0.1 mm.

Anal. Calcd. for $C_{10}H_{23}ONS$: N, 7.18. Found: N, 6.90.

γ-Diethylaminopropyl γ-Chloropropyl Sulfide. By the method described for the preparation of β-diethylaminoethyl γ-chloropropyl sulfide (p. 11), 89 g. (0.43 mole) of γ-diethylaminopropyl γ-hydroxypropyl sulfide was converted to the chloride with 102 g. (0.86 mole) of thionyl chloride. The yield was 70 g. (74%) of a colorless oil boiling at 95-97°/0.1 mm., n_D^{20} 1.4890, d_4^{20} 0.9980. M. R. calcd. 64.87; found 64.45.

Anal. Calcd. for $C_{10}H_{22}NClS$: N, 6.28. Found: N, 6.00.

γ-Diethylaminopropyl β-Hydroxyethyl Sulfide. From 85 g. (0.57 mole) of γ-diethylaminopropyl chloride, 44.5 g. (0.57 mole) of

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16. Gilman and Shirley, J. Am. Chem. Soc., 66, 888 (1944).

β-hydroxyethyl mercaptan and 13.1 g. (0.57 g. atom) of sodium in 300 ml. of absolute ethanol, this hydroxysulfide was prepared by the method described for its isomer (p. 11). The yield of this sulfide was 85 g. (77%) of material boiling at 100-102°/0.1 mm.

Anal. Calcd. for $C_9H_{21}ONS$: N, 7.73. Found: N, 7.55.

γ-Diethylaminopropyl β-Chloroethyl Sulfide. Eighty-five grams (0.445 mole) of γ-diethylaminopropyl β-hydroxyethyl sulfide was added to 107 g. (0.9 mole) of thionyl chloride in 200 ml. of chloroform at 0°. This reaction was carried out in accordance with the method used for the preparation of γ-chloropropyl β-diethylaminoethyl sulfide. The yield was 50 g. (54%) of material boiling at 71-75°/0.1 mm.

Anal. Calcd. for $C_9H_{20}NClS$: N, 6.70. Found: N, 6.56.

A solid hydrochloride was prepared by the addition of ethereal hydrogen chloride to a solution of the sulfide. No attempt was made to purify this salt which was very hygroscopic and very soluble in absolute ethanol.

8-[γ-(γ'-Diethylaminopropylmercapto)-propylamino]-6-methoxyquinoline. A mixture of 22.3 g. (0.1 mole) of γ-diethylaminopropyl γ-chloropropyl sulfide and 17.4 g. (0.1 mole) of 6-methoxy-8-aminoquinoline was heated on a boiling water bath for one hour. This melt was then heated with an oil bath at 100-110° for three hours longer. The reaction product was dissolved in water and made strongly basic with ammonium hydroxide while maintaining the temperature below 15°. The oil was extracted with ether, dried and distilled to give 10 g. of material boiling at 90-212°/0.1 mm. which was largely 6-methoxy-8-aminoquinoline. The higher boiling fraction consisted of 17 g. (44%) of a yellow viscous

oil boiling at 215-220°/0.1 mm. Redistillation gave 13 g. of product boiling at 215-220°/0.1 mm.

Anal. Calcd. for $C_{20}H_{31}ON_3S$: N, 11.63. Found: N, 11.60.

8-[γ-(γ'-Diethylaminopropylmercapto)-propylamino]-6-methoxyquinoline Dihydrochloride. The dihydrochloride was prepared in an absolute ethanol-ether solution of hydrogen chloride. This orange compound was recrystallized from absolute ethanol to a constant melting point of 128-130°.

Anal. Calcd. for $C_{20}H_{33}ON_3Cl_2S$: N, 9.70. Found: N, 9.74.

8-[β-(γ-Diethylaminopropylmercapto)-ethylamino]-6-methoxyquinoline. A mixture of 15 g. (0.066 mole) of γ-diethylaminopropyl β-chloroethyl sulfide hydrochloride, 8.7 g. (0.05 mole) of 6-methoxy-8-aminoquinoline and 5 ml. of absolute ethanol was slowly heated in an oil bath to 110°. The bath temperature was held at 110° for six hours, and then at 110-115° for five hours longer. The temperature control is very important as higher temperatures gave much lower yields. The reaction product was dissolved in water and the solution was made strongly basic with concentrated ammonia solution. The oil was extracted with ether, dried over anhydrous sodium sulfate, and distilled to give 9 g. of material boiling at 50-150°/0.1 mm., and 7 g. (41%) of product boiling at 205-210°/0.1 mm.

Anal. Calcd. for $C_{19}H_{29}ON_3S$: N, 12.10. Found: N, 12.08.

8-[β-(γ-Diethylaminopropylmercapto)-ethylamino]-6-methoxyquinoline Dihydrochloride. The dihydrochloride was prepared in an ethereal hydrogen chloride solution. This compound was recrystallized from absolute ethanol to a constant melting point of 164-165°.

Anal. Calcd. for $C_{19}H_{31}ON_3Cl_2S$: N, 10.00. Found: N, 9.75.

β-Diethylaminoethyl Mercaptan.[10, 17, 18] Hydrogen sulfide was bubbled through 340 g. (1.4 moles) of melted sodium sulfide nonohydrate until the solution was thoroughly saturated. To this solution, 90 g. (0.67 mole) of freshly distilled β-diethylaminoethyl chloride (p. 11) was added. With vigorous stirring, this mixture was refluxed for one hour. After cooling, the solution was extracted with ether and the ethereal solution was dried over anhydrous sodium sulfate. The product was distilled at reduced pressure to give 51 g. (57%) of material boiling at 62-65°/21 mm., n_D^{20} 1.468, d_4^{20} 0.8751. The yields and purity of this mercaptan varied considerably (p. 54).

β-Diethylaminoethyl Mercaptan Hydrochloride.[17] Ethanolic hydrogen chloride was added to an absolute ethanolic solution of the free base. The hydrochloride precipitated on cooling, and this material was recrystallized from absolute ethanol-ethyl acetate to a constant melting point of 170-172°.

Anal. Calcd. for $C_7H_{18}NClS$: N, 7.65. Found: N, 7.78.

β-Diethylaminoethyl 2,4-Dinitrophenyl Sulfide Hydrochloride.[17] The mercaptan was added dropwise to 1 g. of 2,4-dinitrochlorobenzene until no further reaction was observed. The solid product was recrystallized from 95% ethanol to a constant melting point of 187-188°.

Anal. Calcd. for $C_{12}H_{18}O_4N_3ClS$: N, 12.51. Found: N, 12.78.

γ-Diethylaminopropyl Mercaptan.[17] This mercaptan has been prepared by the method described above for the corresponding ethyl derivative. The yield, of material boiling at 76-80°/26 mm., was 49%. The constants obtained were: n_D^{20} 1.4450 and d_4^{20} 0.8921 (p. 54).

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17. Gilman, Plunkett, Tolman, Fullhart, and Broadbent, J. Am. Chem. Soc., 67, 000 (1945).
18. Albertson and Clinton, J. Am. Chem. Soc., 67, 1222 (1945).

γ-Diethylaminopropyl 2,4-Dinitrophenyl Sulfide Hydrochloride.[17] This compound was prepared by the method used above for the corresponding ethyl derivative. The product was recrystallized from absolute ethanol to a constant melting point of 143-145°.

Anal. Calcd. for $C_{13}H_{20}O_4N_3ClS$: N, 12.02. Found: N, 11.95.

β-Diethylaminoethyl γ-Aminopropyl Sulfide. A warm solution of 77.3 g. (0.3 mole) of γ-bromopropylphthalimide in 200 ml. of absolute ethanol was added dropwise to 250 ml. of boiling absolute ethanol containing 0.3 mole of sodium β-diethylaminoethyl mercaptide. After the addition, the ethanol was removed by distillation from a steam bath. The residue was diluted with water and extracted with ether. Distillation of the ether solution gave an oily residue weighing 85 g. To this crude product was added 90 ml. of 48% hydrobromic acid. The solution was refluxed for three and one-half hours. On cooling, a white solid precipitated, this material was filtered and washed well with water. The filtrate was neutralized with a concentrated sodium hydroxide solution and the oil that separated was extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and distilled at reduced pressure to give 22 g. (39%) of product boiling at 93-95°/0.1 mm.

Prior to this preparation, β-diethylaminoethyl γ-aminopropyl sulfide was found in the patent literature.[19] After the work was completed in this laboratory, Clinton and co-workers[20] described the preparation of this compound in 48% yield.

19. Ger. Patent 450,254 (1935) [Chem. Zentr., I, 384 (1937)].

20. Clinton and co-workers, J. Am. Chem. Soc., 67, 594 (1945).

9-[γ-(β-Diethylaminoethylmercapto)-propylamino]-6-chloro-2-methoxyacridine. A solution of 11 g. (0.057 mole) of β-diethylaminoethyl γ-aminopropyl sulfide and 13.9 g. (0.5 mole) of 6,9-dichloro-2-methoxyacridine in 60 g. of phenol was heated in a boiling water bath for two hours. The reaction mixture was poured into a dilute sodium hydroxide solution, and the oil was extracted with ether. The ether extract was washed once with a dilute sodium hydroxide solution. The ether was removed by distillation, and the residue steam distilled to remove any unreacted β-diethylaminoethyl γ-aminopropyl sulfide. The non-volatile material was extracted with ether, and the upper layer was separated. After distilling the ether, a solid crystalline mass remained. A small amount of this material was recrystallized from petroleum ether (b.p., 80-110°)-benzene to give a product melting at 62-64°.

Anal. Calcd. for $C_{23}H_{30}ON_3ClS$: N, 9.73. Found: N, 9.85.

The main portion of the product was dissolved in absolute ethanol and precipitated from solution as the dihydrochloride with ethereal hydrogen chloride. This material weighed 20 g. (80%) and melted at 247-249°. One recrystallization of this product from 95% ethanol gave 13.5 g. of material melting at 252-254°.

Anal. Calcd. for $C_{23}H_{32}ON_3Cl_3S$: N, 8.35. Found: N, 8.25.

3-[γ-(γ'-Diethylaminopropylmercapto)-propylamino]-trifluoromethylbenzene. A mixture of 7.9 g. (0.05 mole) of 3-trifluoromethylaniline (p. 23) and 11.3 g. (0.05 mole) of γ-diethylaminopropyl γ-chloropropyl sulfide was heated slowly in an oil bath to 110°. The temperature remained at 110-125° for eight hours, and then it was held at 120° for twenty-four hours. The mixture was dissolved in water and made strongly basic with concentrated ammonium hydroxide. The product was extracted with ether, dried over anhydrous sodium sulfate, and

distilled to give 7 g. (40%) of material boiling at 173-175°/0.1 mm.

Anal. Calcd. for $C_{17}H_{27}N_2F_3S$: N, 8.09. Found: N, 8.22.

The dihydrochloride was prepared in an ethereal solution of hydrogen chloride. The product was recrystallized from ether-absolute ethanol to a constant melting point of 123-124°.

Anal. Calcd. for $C_{17}H_{29}N_2Cl_2F_3S$: Cl, 16.90. Found: Cl, 17.00.

β-Diethylaminoethyl γ-(2,5-Dimethyl-1-pyrryl)-propyl Sulfide. A solution of 9.0 g. (0.047 mole) β-diethylaminoethyl γ-aminopropyl sulfide, 5.7 g. (0.05 mole) of acetonylacetone, 1 ml. of acetic acid, and 30 ml. of absolute ethanol was refluxed gently for three hours. The solution was diluted with water and distilled at reduced pressure to remove most of the ethanol. The product was extracted with ether, dried over anhydrous sodium sulfate, and distilled at reduced pressure to give 5.5 g. (41%) of product boiling at 143-145°/0.1 mm. A solid hydrochloride could not be prepared.

Anal. Calcd. for $C_{15}H_{28}N_2S$: N, 10.43. Found: N, 10.42.

β-Hydroxyethyl γ-Chloropropyl Sulfide. To a solution of 23 g. (1.0 g. atom) of sodium in 300 ml. of absolute ethanol, 78 g. (1.0 mole) of β-hydroxyethyl mercaptan in 100 ml. of absolute ethanol was slowly added. With vigorous stirring at 20°, 173 g. (1.1 moles) of γ-chloropropyl bromide in 50 ml. of absolute ethanol was added over a period of one hour. The ethanol was removed by distillation, and the residue was dissolved in ether. This solution was filtered, and the filtrate distilled to give 130 g. (85%) of material boiling at 93-96°/0.1 mm., n_D^{20} 1.5140, d_4^{20} 1.1766, M.R. calcd. 40.29; found 39.75.

Anal. Calcd. for $C_5H_{11}OClS$: Cl, 22.97. Found: Cl, 22.90.

β-Acetoxyethyl γ-Chloropropyl Sulfide. A mixture of 30.8 g. (0.20 mole) of β-hydroxyethyl γ-chloropropyl sulfide and 22.4 g. (0.22 mole) of acetic anhydride was refluxed gently for one hour. The reaction was vigorous at first. The acetic acid was removed by distillation, and the residue was distilled at reduced pressure to give 37 g. (94%) of material boiling at 85-95°/0.1 mm. Redistillation gave 35 g. boiling at 86-87°/0.1 mm., n_D^{20} 1.4879, d_4^{20} 1.1531, M.R. calcd. 48.96; found 49.28.

Anal. Calcd. for $C_7H_{13}O_2ClS$: S, 16.28. Found: S, 16.03.

Oxidation of β-Acetoxyethyl γ-Chloropropyl Sulfide. To 30.6 g. (0.2 mole) of β-hydroxyethyl γ-chloropropyl sulfide, 30 ml. of acetic acid, and 40 g. of acetic anhydride, was slowly added 68 g. (0.6 mole) of 30% hydrogen peroxide. After warming on the steam bath, the reaction proceeded vigorously. The solution was heated for three hours on the steam bath, and then the low boiling material was removed by distillation from a hot water bath at reduced pressure. The residue was a light yellow viscous oil which weighed 36 g. (95%). An attempt to distill this product at 0.1 mm. pressure gave only decomposition products. Crystallization by cooling and scratching in various organic solvents failed. An attempt to distill the same product prepared in a similar experiment failed when the distillation was carried out at 0.01-0.001 mm. During this distillation only low boiling decomposition products were collected. The product obtained before distillation was never pure enough to give a correct analysis.

The oxidation of the β-hydroxyethyl γ-chloropropyl sulfide with hydrogen peroxide, by a method similar to that described for the oxidation of the corresponding acetylated compound, failed to give a product which could be purified.

Attempted Preparation of α-Chloromethyl β-Diethylaminoethyl Sulfide. A mixture of 16.9 g. (0.1 mole) of β-diethylaminoethyl mercaptan hydrochloride (p. 15) and 3.0 g. (0.11 mole) of paraformaldehyde was suspended in 60 ml. of anhydrous ether. At 0°, a rapid stream of anhydrous hydrogen chloride was bubbled through the suspension for ten minutes. At the end of this period, the suspended material was rather fluid, and the flask was tightly stoppered and placed in the ice-box for three hours. The ether was decanted, and the oily product was washed twice with 25 ml. portions of ether. An attempt to free the base and distill the product failed to give a pure compound.

In another experiment, the product was treated with 37 g. (0.5 mole) of diethylamine, while cooling in an ice bath. After all of the amine was added, the mixture was refluxed gently for one hour. The solution was poured into water and neutralized with ammonium hydroxide. The oil was extracted with two 75-ml. portions of ether. The product was dried over anhydrous sodium sulfate, and this material was distilled to give 8 g. of colorless oil boiling at 60-90°/20 mm. and 7 g. boiling at 90-140°/0.3 mm. The higher boiling fraction was redistilled to give 3 g. of material boiling at 90-95°/0.3 mm. A solid hydrochloride could not be prepared, and none of the products was identified.

β-Diethylaminoethyl Mercaptan and Epichlorohydrin. In accordance with the procedure described by Gilman and Woods,[10] epichlorohydrin was treated with sodium diethylaminoethyl mercaptide. To 500 ml. of toluene and 19 g. (0.83 mole) of sodium, 110 g. of β-diethylaminoethyl mercaptan was added dropwise. After the addition, the hot solution was decanted from a small amount of sodium. The sodium mercaptide precipitated from the solution on cooling, and this thick sludge of mercaptide was added slowly to 66 g. (0.9 mole) of epichlorohydrin in 200 ml. of toluene.

This addition was carried out with cooling by an ice bath and vigorous mechanical stirring. After the addition was complete, stirring was continued for one-half hour. The toluene was removed by distillation from a steam bath at reduced pressure with stirring. The residue was poured into ice water and extracted with two portions of ether. This product was dried over anhydrous sodium sulfate, and then distilled at reduced pressure to give 78 g. (54%) of material boiling at 72-82°/0.1 mm., n_D^{20} 1.4989.

1-(β-Diethylaminoethylmercapto)-2,3-epoxypropane and Diethylamine. A solution of 34 g. (0.179 mole) of the freshly distilled epoxy compound and 22 g. (0.3 mole) of diethylamine was refluxed for seven hours. This mixture was distilled to give 18 g. of diethylamine and 33 g. of material boiling at 82-85°/0.1 mm. Before the reaction, the starting epoxypropane distilled at 79-82°/0.1 mm. The boiling points indicate that starting material was recovered almost quantitatively.

A similar experiment was tried in which ethereal hydrogen chloride was added to the solution of the reactants until a small amount of precipitate remained suspended in the solution. This mixture was gently refluxed for seventeen hours. Distillation of the solution gave 20 g. of diethylamine and 34 g., a quantitative recovery, of the 1-(β-diethylaminoethylmercapto)-2,3-epoxypropane.

1-(β-Diethylaminoethylmercapto)-2,3-epoxypropane and 8-(N-Lithio)-amino-6-methoxyquinoline. In a 250 ml. three-necked flask equipped with a mechanical stirrer and a condenser, was placed 8.7 g. (0.05 mole) of 6-methoxy-8-aminoquinoline in 75 ml. of anhydrous ether. At 0°, 0.05 mole of methyllithium in 36 ml. of anhydrous ether was added dropwise under an atmosphere of nitrogen. The addition required ten minutes, and approximately the theoretical amount of gas was given off by the

reaction. A yellowish-green precipitate formed during the addition of the methyllithium. After the addition was complete, the mixture was stirred for ten minutes, and color tests I[21] and IV[22] were negative. To this suspension 9.5 g. (0.05 mole) of 1-(β-diethylaminoethylmercapto)-2,3-epoxypropane in 50 ml. of anhydrous ether was added dropwise at 0°. During the addition, the precipitate dissolved, and the color of the solution changed to a dark green. Stirring was continued for one-half hour after the addition was complete, and then the product was hydrolyzed by the addition of water to the solution. Ethereal hydrogen chloride was added to the ether layer after drying over anhydrous sodium sulfate. The hydrochloride that precipitated was identified (mixed m. p.) as 6-methoxy-8-aminoquinoline dihydrochloride, and 88% of this starting material was recovered.

6-Amino-7-trifluoromethylquinoline and γ-Diethylaminopropyl γ-Chloropropyl Sulfide. A mixture of 5.25 g. (0.025 mole) of 6-amino-7-trifluoromethylquinoline (p. 26) and 5.6 g. (0.025 mole) of γ-diethylaminopropyl γ-chloropropyl sulfide was heated slowly to 110°. The temperature remained at 110-115° for fifteen hours. The material from the reaction was isolated and identified (mixed m. p.) as the starting quinoline compound. Considerable decomposition occurred during the heating period, and only 60% of the starting quinoline compound was recovered.

In a second experiment the reactants were heated at 110-120° for thirty-six hours. Only starting material and decomposition products were obtained.

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21. Gilman and Schulze, J. Am. Chem. Soc., 47, 2002 (1925).

22. Gilman and Woods, J. Am. Chem. Soc., 65, 435 (1943).

Trifluoromethylbenzene. This trifluoromethyl derivative was prepared from benzotrichloride and antimony trifluoride in accordance with the directions described by Martin.[23] The yield of material boiling at 103-105° was 69%, and 7% of less pure material boiling at 105-110° was obtained.

m-Trifluoromethylaniline.[23] Trifluoromethylbenzene was nitrated with a sulfuric acid-fuming nitric acid mixture, and the crude nitrated product was reduced directly with iron and sulfuric acid. The yields were comparable to those described by Martin.

7-Trifluoromethylquinoline.[11] The Skraup synthesis with m-trifluoromethylaniline gave a 35% yield of the 7-isomer. Sixty-five grams (0.4 mole) of m-trifluoromethylaniline, 57 g. (0.4 mole) arsenic acid, 105 g. (1.3 moles) of glycerol, and 110 g. of concentrated sulfuric acid gave 27 g. (35%) of the product boiling at 125-128°/25 mm. This product solidified and crystallized from petroleum ether (b. p., 80-110°) to give material melting at 66-68°. The 5-trifluoromethylquinoline was not isolated.

7-Trifluoromethylquinoline Picrate. This derivative was prepared in the usual manner and recrystallized from ethanol to a constant melting point of 220-221°.

Anal. Calcd. for $C_{16}H_9O_7N_4F_3$: N, 13.14. Found: N, 13.10.

m-Trifluoromethylacetanilide. One hundred ml. of acetic anhydride was added very slowly to 100 g. (0.62 mole) of trifluoromethylaniline, and the mixture was warmed on a steam bath for five minutes. This solution was poured into 500 ml. of ice water, and the solid was filtered

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23. Unpublished studies by G. A. Martin, Jr.

to give 100 g. (79%) of product. One recrystallization from benzene-petroleum ether (b. p.,80-110°) gave material melting at 103-104°.

Nitration of m-Trifluoromethylacetanilide in Sulfuric Acid. In accordance with the directions described by Rouche,[24] 60 g. of nitric acid (sp. gr. 1.50) in 100 ml. of concentrated sulfuric acid was added slowly to 100 g. (0.49 mole) of m-trifluoromethylacetanilide in 500 ml. of concentrated sulfuric acid at -5°. After completing the addition, the mixture was stirred for three hours longer, and then the clear acid solution was poured into 2 l. of crushed ice. Standing for twelve hours resulted in a solid yellow mass which was collected by filtration. This product was hydrolyzed by refluxing four hours in 1500 ml. of 8% sodium hydroxide solution. On cooling, the crude product solidified and this material was filtered and dried to give 90 g. (89%) of the crude solid. This material was dissolved in a minimum of 50% ethanol, and after cooling, the material crystallized to give 60 g. (59%) of a solid melting at 124-126°. Thirty grams (29%) of material melting at 80-90° was recovered from the filtrate. Pure material was obtained from the higher melting product by one extraction of hot petroleum ether (b. p., 80-110°) followed by a crystallization from benzene. The pure material melting at 126-127° was 3-trifluoromethyl-4-nitroaniline, and the yield was 44 g. (43%). The lower melting isomers were not separated from the less pure material and the mother liquors.

Nitration of m-Trifluoromethylacetanilide With Acetyl Nitrate.[24] One hundred and twenty grams (0.75 mole) of trifluoromethylacetanilide was nitrated in portions of 15 g. each to avoid handling large quantities of acetyl nitrate. Fourteen grams of ice-cold nitric acid (sp. gr. 1.50)

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24. Rouche, Bull. sci. acad. roy. Belg., 13, 346 (1927).

was added very slowly to 20 g. of acetic anhydride at 0°. With continued cooling, 15 g. of the solid m-trifluoromethylacetanilide was added slowly, and as the solid dissolved, a slight coloring of the solution occurred. Fifteen minutes after the last of the acetanilide was added, the solution was poured upon crushed ice. The resulting red paste was filtered, and most of the water was removed. This crude product was dissolved in hot ethanol, and on cooling the solution, 48 g. (26%) of a colorless material precipitated. One recrystallization from benzene-petroleum ether (b. p., 80-110°) gave 38 g. (21%) of material melting at 168-169°. This compound, 3-trifluoromethyl-2-nitroacetanilide, was hydrolyzed by refluxing for one hour in 500 ml. of 10% sodium hydroxide. Filtration, subsequent to cooling, gave 30 g. (20%) of the free amine melting at 61-62°.

The ethanolic filtrate from the first crystallization was distilled to remove most of the solvent, and the product was hydrolyzed by boiling in a 10% sodium hydroxide solution. Most of the basic solution was decanted from the dark red oil, and this residue was steam distilled. Ten grams of material was volatile with steam, and 25 g. remained in the distillation vessel. The latter material was recrystallized from dilute ethanol to give 3-trifluoromethyl-6-nitroaniline which melted at 100-101°. The more volatile material was largely 3-trifluoromethyl-2-nitroaniline.

7-Trifluoromethyl-6-nitroquinoline. In a 500 ml. three-necked flask equipped with a stirrer and a condenser was placed 41 g. (0.2 mole) of 3-trifluoromethyl-4-nitroaniline, 27 g. (0.2 mole) of arsenic acid, and 53 g. (0.65 mole) of glycerol. While stirring this mixture, 56 g. of concentrated sulfuric acid was added slowly. This addition warmed the solution, but more heat was supplied using a metal bath until the solution began to reflux. Gentle refluxing was continued for two hours,

and then the reaction product was poured into ice. The solid was collected by filtration and air-dried to give 50 g. of material melting at 151-155°. This precipitate was dissolved in 6 N hydrochloric acid solution and the solution was filtered to remove a small amount of insoluble material. The free amine was precipitated by the addition of concentrated ammonium hydroxide. This product was filtered, and after two crystallizations from ethanol 27 g. (56%) of material melting at 164-165° was obtained.

Anal. Calcd. for $C_{10}H_5O_2N_2F_3$: N, 11.57. Found: N, 11.76.

7-Trifluoromethyl-6-aminoquinoline. Sixty grams of stannous chloride ($SnCl_2.2H_2O$) in 50 ml. of concentrated hydrochloric acid was added cautiously to 10 g. (0.04 mole) of 7-trifluoromethyl-6-nitroquinoline in 50 ml. of concentrated hydrochloric acid. A very vigorous reaction resulted, and after the addition was complete, the solution was very hot. Some crystalline product precipitated from the hot solution, and on cooling in an ice bath a voluminous mass separated. After filtering the solid and pressing most of the solution out of the precipitate, the product was suspended in 50 ml. of water and this mixture was made strongly basic by the addition of a concentrated sodium hydroxide solution. The yellow acid suspension changed to grey on neutralization. The basic mixture was filtered, washed well with water, and air-dried. This solid material was refluxed with ethanol for a few minutes in order to extract the amine from small amounts of inorganic material. The hot ethanol was filtered and diluted with water; cooling gave 8 g. (91%) of material melting at 152-153°. This product was recrystallized from benzene-petroleum ether (b. p.,80-110°) to a constant melting point of 154-155°.

Anal. Calcd. for $C_{10}H_7N_2F_3$: N, 13.21. Found: N, 13.48.

Deamination of 7-Trifluoromethyl-6-aminoquinoline. One gram (0.005 mole) of the 7-trifluoromethyl-6-aminoquinoline was diazotized at 0°, using 2.5 ml. of concentrated hydrochloric acid, 200 ml. of water, and 0.4 g. (0.0057 mole) of sodium nitrite. To the cold diazonium solution was added 2 g. of ice-cold 50% hypophosphorous acid. This solution was placed in the ice-box for thirty-eight hours. The small amount of solid that had precipitated was filtered, and then the filtrate was neutralized with ammonium hydroxide. The oil that separated was extracted with three 15-ml. portions of ether. These extracts were combined and dried over anhydrous sodium sulfate, and after the ether was removed by distillation, an oily solid remained. A picrate of this product was prepared, and after one recrystallization from ethanol, this derivative melted at 220-221°. This picrate was identical (mixed m. p.) with the picrate formed from an authentic specimen of 7-trifluoromethylquinoline.

7-Trifluoromethyl-6-(2,5-dimethyl-1-pyrryl)-quinoline. A solution of 5 g. (0.025 mole) of 7-trifluoromethyl-6-aminoquinoline, 3 g. (0.029 mole) of acetonylacetone, 15 ml. of absolute ethanol, and 1 ml. of acetic acid was refluxed for five and one-half hours. Nearly a quantitative yield of starting material was obtained from the mixture.

In another experiment, 5 g. (0.025 mole) of the amine and 6 g. (0.058 mole) of acetonylacetone with one drop of concentrated hydrochloric acid was refluxed for four hours. Two layers resulted which indicated that water had been produced during the reaction. No solid material could be obtained by attempted crystallizations from ethanolic solutions. The crude oily product was combined with the products from two other similar reactions. This material [the combined products from three different experiments, using a total of 16 g. (0.075 mole) of

amine and 15 g. (0.13 mole) of acetonylacetone_7 was distilled under reduced pressure to give 10 g. (46%) of yellow oil boiling at 135-138°/1.0 mm. This oil crystallized after standing a short time, and the product was recrystallized from aqueous ethanol to give a colorless product melting at 86-87°.

Anal. Calcd. for $C_{16}H_{13}N_2F_3$: N, 9.66. Found: N, 9.90.

7-Trifluoromethyl-6-(2,5-dimethyl-1-pyrryl)-quinoline Picrate. This picrate was prepared in an ethanolic solution, and one crystallization from ethanol gave an orange compound melting at 263-265°.

Anal. Calcd. for $C_{22}H_{16}O_6N_5F_3$: N, 13.92. Found: N, 14.19.

7-Trifluoromethyl-6-(γ-diethylaminopropylamino)-quinoline Picrate. A mixture of 8.5 g. (0.04 mole) of 7-trifluoromethyl-6-aminoquinoline and 10 g. (0.054 mole) of γ-diethylaminopropyl chloride hydrochloride was heated in an oil bath for forty-eight hours at 110-115°, and then the temperature of the bath was raised to 150-155° for twenty-four hours longer. For another twenty-four hour period, the bath temperature was held at 175-180°. This rather severe heating was tried only after the same materials remained unreacted at milder conditions. The melt from this reaction was dissolved in water, and the free base was precipitated with ammonium hydroxide. The oily product was extracted from the aqueous mixture with three portions of ether. The extracts were dried over anhydrous sodium sulfate, and after removing the ether, the product was distilled at reduced pressure to give 2.5 g. (19%) of a dark yellow oil boiling at 160-170°/0.1 mm. This oil did not give the correct nitrogen analysis for the expected product.

This crude product did give a picrate which was purified by recrystallization from ethanol. This derivative was rather insoluble in ethanol and the purified compound melted at 236-238°.

Anal. Calcd. for $C_{23}H_{22}O_6N_6F_3$: N, 15.67. Found: N, 15.60.

Attempted Preparation of 7-Trifluoromethyl-8-nitroquinoline. Forty grams (0.2 mole) of 3-trifluoromethyl-2-nitroaniline, 29 gm. (0.2 mole) of arsenic acid, 53 g. (0.6 mole) of glycerol, and 56 g. of concentrated sulfuric acid was heated four hours at the reflux temperature with vigorous mechanical stirring. This reaction product was poured upon ice to give a black solid which was not soluble in hot ethanol or hot concentrated hydrochloric acid. This material was obviously not the expected product or starting material.

Attempted Preparation of 5-Trifluoromethyl-8-nitroquinoline. By the method described above for the preparation of 7-trifluoromethyl-6-aminoquinoline, 40 g. (0.2 mole) of 3-trifluoromethyl-6-nitroaniline was used in an attempted Skraup synthesis. The mixture was heated four hours with a metal bath at 150-160°, and the product was poured upon ice. Neutralization of the solution gave 35 g. of material melting at 85-95°. This was distilled at 0.2 mm. pressure in an attempt to purify the product, but the distillation failed to yield a pure compound. This impure product was probably a mixture of the expected product and starting 3-trifluoromethyl-6-nitroaniline as very little decomposition occurred.

p-Bromophenylarsonic Acid. In accordance with the method described by Blicke and Webster,[25] rather large quantities of this arsonic acid was prepared.

Five hundred and twenty grams (3.0 moles) of p-bromoaniline was diazotized with 1 l. of concentrated hydrochloric acid, 5 l. of water and 220 g. (3.0 moles) of sodium nitrite. The hydrochloride of the

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25. Blicke and Webster, J. Am. Chem. Soc., 59, 535 (1937).

amine was not soluble in the acid solution, but the diazonium salt was completely dissolved. This cold diazonium solution was added slowly with stirring to a cold solution containing 1100 g. (10.4 moles) of sodium carbonate, 520 g. (4.0 moles) of sodium arsenite, 40 ml. of saturated copper sulfate solution, and 8 l. of water. During the addition, crushed ice was added occasionally in order to keep the temperature below 10°, and ether was added periodically to reduce the foaming. The addition required forty-five minutes, and the solution was stirred two hours after all of the diazonium solution had been added. This mixture was allowed to settle for several hours, and then the solution was filtered. After evaporating the filtrate to a volume of 3 l., the arsonic acid was precipitated by neutralization with concentrated hydrochloric acid. The voluminous solid was filtered and washed with water. This crude acid was dissolved in dilute sodium hydroxide and reprecipitated with dilute hydrochloric acid. After washing well with water and drying the solid at 110°, the yield was 780 g. (91%).

p-Bromophenyldichloroarsine. This dichloroarsine has been prepared from p-bromophenylarsonic acid, hydrogen iodide, and sulfur dioxide,[26] but this preparation was carried out by the modification of a superior method described by Avakian.[27] Seven hundred and eighty ml. of phosphorous trichloride was added very slowly to 780 g. (2.8 moles) of p-bromophenylarsonic acid in 2 l. of refluxing glacial acetic acid. The reaction was very vigorous and the addition was controlled so that a gentle reflux was maintained. This addition required one and one-half hours, and the mixture was refluxed with stirring for two hours longer.

26. Hunt and Turner, J. Chem. Soc., 2670 (1925).

27. Unpublished studies by S. Avakian.

After cooling, the cold solution was poured slowly into 1.5 l. of cold concentrated hydrochloric acid with stirring. The oil, that precipitated and settled to the bottom, was separated from the aqueous acid solution. An attempt to obtain additional product from the acid solution by ether extractions was very unsatisfactory, as the ether was to a large extent miscible with the acetic acid-hydrochloric acid solution. The ether extracts were combined with the crude product and dried over anhydrous sodium sulfate. This product is a vesicant and care must be taken to avoid contact with the skin. The ether was removed by distillation and the residue was distilled at reduced pressure to give 500 g. (61%) of material boiling at 105-110°/0.2 mm.

p-Bromophenyldimethylarsine. This compound was first prepared from p-bromophenylmagnesium bromide and dimethyliodoarsine,[28] but this preparation was carried out by a slight modification of the method described by Avakian.[27] A solution of 378 g. (1.25 moles) of p-bromophenyldichloroarsine in 2 l. of petroleum ether (b. p., 28-35°) was added dropwise to 2.5 l. of two molar methylmagnesium iodide prepared from 5 moles of methyl iodide and 5 g. atoms of magnesium. This reaction was carried out with vigorous stirring and cooling with an ice bath. The heat of reaction was sufficient to maintain a vigorous refluxing while immersed in the cooling bath. Stirring was continued for ten minutes after all of the dichloroarsine had been added, and 500 ml. of water was carefully added. Enough dilute hydrochloric acid was added to dissolve all of the insoluble magnesium salts, and the ether layer was separated, washed well with water, and then dried over anhydrous sodium sulfate. This product was distilled at reduced pressure to give 378 g. (88%) of a colorless liquid boiling at 105-110°/0.2 mm.

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28. Jones and co-workers, J. Chem. Soc., 2287 (1932).

p-Lithiophenyldimethylarsine. Under an atmosphere of dry nitrogen, 26.1 (0.1 mole) of p-bromophenyldimethylarsine in 90 ml. of anhydrous ether was added dropwise to 3.0 g. (0.4 g. atom) of lithium in 100 ml. of absolute ether. This reaction did not start immediately, but after stirring a few minutes with a portion of the bromide, reflux began. The yield based on an acid titration was 88%.

Dimethyl-p-(1,2-dihydro-2-quinolylphenyl)-arsine. With vigorous stirring under an atmosphere of nitrogen, 0.088 mole of p-lithiophenyldimethylarsine was added dropwise at room temperature to 11.4 g. (0.088 mole) of quinoline in 50 ml. of anhydrous ether. The addition of the organometallic compound immediately formed a precipitate. This suspension was stirred at room temperature for two and one-half hours after the addition of the lithium compound was complete. The mixture was hydrolyzed by the addition of water to the reaction flask while stirring rapidly with a mechanical stirrer. Most of the solid dissolved after the hydrolysis, and the upper layer was separated and dried over anhydrous sodium sulfate. The product was distilled at reduced pressure to give 11 g. (42%) of a light yellow oil boiling at 185-190°/0.55 mm.

Anal. Calcd. for $C_{17}H_{18}NAs$: N, 4.50. Found: N, 4.35.

Dimethyl-p-(2-quinolylphenyl)-arsine. The 1,2-dihydroquinoline compound prepared above was warmed with an equal volume of nitrobenzene on a steam bath for one hour. This solution was dissolved in ether, and anhydrous hydrogen chloride was bubbled through the ether. The oil that precipitated was separated from the ether solution and this material was neutralized with ammonium hydroxide to give a colorless solid. One crystallization of this material from dilute ethanol gave the pure product melting at 65-66°.

Anal. Calcd. for $C_{17}H_{16}NAs$: N, 4.53. Found: N, 4.48.

Dimethyl-p-(2-quinolylphenyl)-arsine Picrate. The picrates prepared by the usual method from the dihydroquinoline product and the oxidized product, were identical. This derivative melted at 172-173°.

Anal. Calcd. for $C_{23}H_{19}O_7N_4As$: N, 10.39. Found: N, 10.38.

Dimethyl-p-(8-methyl-2-quinolylphenyl)-arsine. In a manner similar to that described above, one tenth of one mole of p-lithiophenyldimethylarsine was added dropwise to 14.3 g. (0.1 mole) of 8-methylquinoline in anhydrous ether. This addition resulted in a color change, but no precipitate formed. The solution was stirred one-half hour after the addition was complete. This solution was hydrolyzed, and 20 ml. of nitrobenzene was added to the ether extract. After drying the ethereal solution over anhydrous sodium sulfate, the product was distilled to give 6 g. (19%) of product boiling at 129-130°/0.1 mm. Decomposition was evident during the distillation.

Anal. Calcd. for $C_{18}H_{18}NAs$: N, 4.35. Found: N, 4.45.

Dimethyl-p-(8-methyl-2-quinolylphenyl)-arsine Picrate. A picrate was prepared by the conventional method and after recrystallization from ethanol this derivative melted at 129-130°.

Anal. Calcd. for $C_{24}H_{19}O_7N_4As$: N, 10.14. Found: N, 10.05.

Dimethyl-p-(7-methyl-2-quinolylphenyl)-arsine. By the method described above for the preparation of related compounds, 0.58 mole of p-lithiophenyldimethylarsine was added to 7.2 g. (0.05 mole) of 7-methylquinoline. This reaction gave no precipitate during the addition of the organometallic compound to the quinoline compound. The solution was hydrolyzed with water, and the upper layer was separated and dried over anhydrous sodium sulfate. During the drying period 20 ml. of nitrobenzene was added to the ethereal solution. The ether and nitrobenzene were removed by distillation, and the residue was distilled at

reduced pressure to give 4 g. (25%) of material boiling at 140-145°/0.15 mm. There was considerable decomposition during the distillation. Decomposition was often observed in distillations of this type of compound, and the yields were always lower when the product was distilled.

Anal. Calcd. for $C_{18}H_{18}NAs$: N, 4.35. Found: N, 4.60.

Dimethyl-p-(7-methyl-2-quinolylphenyl)-arsine Picrate. This picrate was prepared in the usual manner. Repeated recrystallizations from ethanol gave a derivative melting at 177-177.5°.

Anal. Calcd. for $C_{24}H_{19}O_7N_4As$: N, 10.43. Found: N, 10.40.

Dimethyl-p-(6-chloro-2-quinolylphenyl)-arsine. In accordance with the procedure described above, 0.58 mole of p-lithiophenyldimethylarsine was added to 8.1 g. (0.05 mole) of 6-chloroquinoline to give a voluminous precipitate. The mixture was stirred for ten minutes, and then water was added slowly to hydrolyze the mixture. The product was isolated by the method used for related compounds, and after the distillation of nitrobenzene at reduced pressure, the residue in the distillation flask solidified. This crude undistilled product weighed 13 g. (74%), and after one recrystallization from ethanol, 8 g. (45%) of material melting at 120-121° was obtained. A small amount of this product was recrystallized to a constant melting point of 123.5-124°.

Anal. Calcd. for $C_{17}H_{15}NClAs$: N, 4.08. Found: N, 4.34.

Dimethyl-p-(6-chloro-2-quinolylphenyl)-arsine Picrate. A picrate prepared in the conventional manner melted at 149-150°.

Anal. Calcd. for $C_{23}H_{18}O_7N_4ClAs$: N, 9.77. Found: N, 10.05.

Dimethyl-p-(5,6-benzo-2-quinolylphenyl)-arsine. Ten grams (0.05 mole) of 5,6-benzoquinoline and an equal molar amount of p-lithiophenyldimethylarsine were reacted in a manner similar to that described above.

The addition of the organometallic compound resulted in an orange precipitate. The product was isolated as a solid in a manner similar to that used for the 6-chloroquinoline derivative. The crude solid was recrystallized from ethanol to give 10 g. (55%) of material melting at 266-268°. Dioxane was also used successfully as a solvent for crystallization.

Anal. Calcd. for $C_{21}H_{18}NAs$: N, 3.87. Found: N, 3.68.

Dimethyl-p-(5,6-benzo-2-quinolylphenyl)-arsine Picrate. The picrate prepared in ethanol gave a light yellow compound melting at 176-178°.

Anal. Calcd. for $C_{27}H_{21}O_7N_4As$: N, 9.49. Found: N, 9.68.

Dimethyl-p-(2-pyridylphenyl)-arsine. Under an atmosphere of dry nitrogen, 0.09 mole of p-lithiophenyldimethylarsine was added dropwise to 10 g. (0.125 mole) of anhydrous pyridine in absolute ether. A precipitate formed during the addition. A slow stream of air, previously passed through a drying column, was introduced above the mixture. The air was passed over this suspension for sixteen hours while the mixture was stirred. At the beginning of the oxidation, the solid precipitate became dark, but as the oxidation proceeded, the color of the solid changed to light yellow. This suspension was hydrolyzed, and the ethereal layer was separated and dried over anhydrous sodium sulfate. After the removal of the ether and the excess pyridine, the product was distilled at reduced pressure to give 8 g. (35%) of a light yellow liquid boiling at 155-159°/0.1 mm.

Anal. Calcd. for $C_{13}H_{14}NAs$: N, 5.40. Found: N, 5.44.

Dimethyl-p-(2-pyridylphenyl)-arsine Picrate. This derivative prepared and recrystallized from ethanol gave a yellow crystalline solid melting at 150-151°.

Anal. Calcd. for $C_{19}H_{17}O_7N_4As$: N, 11.47. Found: N, 11.60.

p-Dimethylaminophenyl-p'-dimethylarsinophenylcarbinol. Twenty-six grams (0.1 mole) of p-bromophenyldimethylarsine in 100 ml. of anhydrous ether was added to a suspension of 2.4 g. (0.1 g. atom) of magnesium. This mixture was refluxed for two and one-half hours, and the magnesium very slowly disappeared. After all of the magnesium had reacted, 13.5 g. (0.09 mole) of p-dimethylaminobenzaldehyde in a minimum of ether was added dropwise to the Grignard reagent. The reaction mixture was stirred for fifteen minutes after completing the addition of the aldehyde. Hydrolysis of the product was accomplished by the addition of a dilute ammonium chloride solution. The ether layer was separated, and the removal of the solvent left a yellow waxy solid weighing 20 g. (70%). Recrystallization from absolute ethanol-petroleum ether (b. p., 80-110°) gave an analytical sample melting at 89-90°.

Anal. Calcd. for $C_{17}H_{22}ONAs$: N, 4.23. Found: N, 4.28.

p-Dimethylaminophenyl 3-Quinolyl Ketone. p-Dimethylaminophenyllithium was prepared from 3 g. (0.43 mole) of lithium and 30 g. (0.15 mole) of p-dimethylaminobromobenzene. The yield of the lithium compound was 95% as calculated from an acid titration. The solution of this organolithium compound was added dropwise to 20 g. (0.14 mole) of 3-cyanoquinoline in ether solution. A red precipitate formed as the lithium compound reacted with the quinoline compound. The suspension was stirred for five minutes after the addition was complete. The mixture was hydrolyzed by the careful addition of water to the ether suspension with vigorous stirring. The ether extract was separated and steam distilled to remove all volatile material. The residue was dissolved in 20% hydrochloric acid and heated on the steam bath for twelve hours. After cooling the acid solution, the base was precipitated with ammonium hydroxide. The product, a sticky semi-solid at room

temperature, was dissolved in ether and dried over anhydrous sodium sulfate. The ether was removed, and the residue was distilled at reduced pressure to give a main fraction weighing 10 g. (26%) and boiling at 210-240°/0.1 mm. This compound was recrystallized from benzene to give a compound melting at 147-148°.

Anal. Calcd. for $C_{18}H_{16}ON_2$: N, 10.13. Found: N, 10.10.

Oxime of p-Dimethylaminophenyl 3-Quinolyl Ketone. This derivative was prepared by heating hydroxylamine hydrochloride, sodium acetate, and the ketone in 50% ethanol. The product, a pale yellow solid recrystallized from ethanol, melted at 247-249°.

Anal. Calcd. for $C_{18}H_{17}ON_3$: N, 14.46. Found: N, 14.42.

3-Cyanoquinoline and p-Lithiophenyldimethylarsine. Under an atmosphere of dry nitrogen, 0.065 mole of p-lithiophenyldimethylarsine was added dropwise to 10 g. (0.065 mole) of 3-cyanoquinoline. The suspension was stirred for twenty minutes after the addition was complete. There was a bulky precipitate formed during the addition, and the reaction was exothermic. This mixture was hydrolyzed with water. The ethereal extract was separated, and the solvent was removed by distillation to leave a viscous oil. The material was refluxed with 20% hydrochloric acid for twenty-four hours. This treatment gave, after neutralization, a red glass which could not be crystallized. This material was treated for eight hours in boiling 10% sodium hydroxide, but the product appeared to be unchanged. After an attempt to crystallize the product failed, distillation at 1.0 mm. pressure was tried. This distillation gave only decomposition products.

3-Bromoquinoline. This compound was prepared several times in accordance with the method described by Spatz.[29] The method developed by

29. Unpublished results by S. M. Spatz.

Spatz was a modification of that reported by Claus and Collischon.[30] A slight excess of 48% hydrobromic acid was added to 200 g. (1.56 moles) of quinoline, and the solution was evaporated to dryness under reduced pressure with heating on a boiling water bath. Two hundred and forty-nine grams (1.56 moles) of bromine in 200 ml. of chloroform was added slowly to the quinoline hydrobromide dissolved in 350 ml. of warm chloroform. During the addition, a red oil precipitated, and on cooling the mixture, a hard red crystalline solid formed. This solid was filtered and washed well with chloroform. Two hundred grams of this air-dried red solid was placed in a 600 ml. beaker and heated with a graphite bath to 180-200° for a one-half hour period. During this period, the melt was stirred by hand and toward the end of the heating period crystallization of the 3-bromoquinoline hydrobromide began. The heating was discontinued when the melt completely solidified. This crystalline mass was suspended in water, and the free base liberated by the addition of dilute sodium hydroxide solution. The oily product was extracted with petroleum ether (b. p., 60-68°). The solvent was removed by distillation from a steam bath, and the residue was distilled at reduced pressure to give 120 g. (39%) of material boiling at 110-111°/1.0 mm.

The 3-bromoquinoline hydrobromide can be recrystallized from acetic acid. Several preparations of 3-bromoquinoline were made, and the yields varied from 39-45%, with as much as 400 g. of 3-bromoquinoline prepared in one experiment.

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30. (a) Claus and Collischon, Ber., 19, 2763 (1886). (b) Edinger, Ber., 29, 2459 (1896).

3-Cyanoquinoline. Gilman and Spatz[31] prepared 3-cyanoquinoline from a modified method described by Jansen and Wibaut.[32] The method developed by the former was used in this experiment. In a 200 ml. Claisen flask attached to an air condenser, was placed 121 g. (0.58 mole) of 3-bromoquinoline and 81 g. of cuprous cyanide. The flask was heated with a free flame until fusion of the mixture began, and at that time the system was evacuated to approximately 1 mm. The distillation was carried out as rapidly as possible with heating by a direct flame. The crude 3-cyanoquinoline solidified readily in the condenser and receiving vessel. This product weighed 89 g. and one recrystallization from absolute ethanol-petroleum ether (b. p., 60-68°) gave 74 g. (83%) of material melting at 105-106°.

3-Quinolinecarboxylic Acid. In accordance with the procedure described by Gilman and Spatz[31], the 3-cyanoquinoline was hydrolyzed with 70% sulfuric acid. Sixty grams (0.39 mole) of the 3-cyanoquinoline and 120 ml. of 70% sulfuric acid was refluxed four hours to give a quantitative yield (70 g.) of crude 3-quinolinecarboxylic acid. This acid was used in the crude form for the preparation of the ester.

Ethyl 3-Quinolinecarboxylate. The esterification of the 3-quinolinecarboxylic acid with sulfuric acid and absolute ethanol was described by Gilman and Spatz,[31] but the yields were very low (35%). In an effort to improve the yield of this ester, the method of hydrogen chloride-absolute ethanol was used in this preparation. Dry hydrogen chloride was bubbled through a suspension of 54 g. (0.3 mole) of the acid in 540 ml. of absolute ethanol until the mixture was saturated. With stirring and the continuous introduction of hydrogen chloride, the mixture was refluxed

31. Gilman and Spatz, J. Am. Chem. Soc., 63, 1553 (1941).

32. Jansen and Wibaut, Rec. trav. chim., 56, 709 (1937).

for ten hours. Most of the solvent was removed by distillation at reduced pressure from a steam bath, and the residue was dissolved in water. This solution was poured very slowly into an excess of ice-cold sodium carbonate solution. The precipitate was filtered and washed well with water to give 42 g. (65%) of product melting at 67-68°.

Methyl 3-Quinolineimidocarboxylate. Anhydrous hydrogen chloride was passed into a solution of 4 g. (0.026 mole) of 3-cyanoquinoline in 200 ml. of absolute methanol. When the methanol solution was saturated, this solution was allowed to stand at room temperature overnight. Most of the solvent was removed to give 4 g. (70%) of material melting at 253-255°. Two grams of this product was dissolved in water, and the free base was precipitated by the addition of cold dilute sodium hydroxide. This solid melted at 194-195°, and crystallization from methanol-petroleum ether (b. p., 60-68°) gave the pure compound melting at 195-196°.

Anal. Calcd. for $C_{11}H_{10}ON_2$: N, 15.05. Found: N, 15.29.

Methyl 3-Quinolineimidocarboxylate and Ammonia. An excess of liquid ammonia was added to 16 g. (0.086 mole) of the imido ester and 100 ml. of absolute methanol. After standing for a few hours, a solid separated which melted at 195-197°. The solid was identified as starting ester (mixed m. p.). This material was then treated with more liquid ammonia, but again only starting ester was obtained.

Ethyl 3-Quinolinecarbonyl Acetate. Nandi[33] first prepared this ester by a similar method, but the β-keto ester was not isolated and purified. This worker attempted to distill the ester, but the material decomposed on attempted purification.

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33. Nandi, Proc. Indian Acad. Sci., 12A, 1 (1940) [C.A., 34, 7918 (1940)].

Twenty grams (0.29 mole) of anhydrous, alcohol-free, sodium ethoxide, 26 g. (0.29 mole) of freshly distilled ethyl acetate and 40 g. (0.20 mole) of ethyl 3-quinolinecarboxylate in 40 ml. of anhydrous benzene was refluxed for fourteen hours. After cooling, the reaction mixture was poured into 90 ml. of cold 10% sodium hydroxide solution. The yellow solid was filtered, and after air-drying, the material was dissolved in 150 ml. of hot glacial acetic acid. After filtration from small amounts of tarry material, the filtrate was diluted with 400 ml. of cold water to give a yellow solid. The yield of the solid was 38 g. (78%). An analytical sample, purified by repeated crystallizations from absolute ethanol-petroleum ether (b. p., 60-68°), melted at 85-87°.

Anal. Calcd. for $C_{14}H_{13}O_3N$: N, 5.81. Found: N, 5.97.

Methyl 3-Quinolyl Ketone. The crude β-keto ester from the experiment above was heated with 200 ml. of 25% sulfuric acid until the evolution of gas ceased. The free ketone was obtained by the neutralization of the acid solution. The product was filtered, dried, and recrystallized from petroleum ether (b. p., 60-68°) to give 25 g. (95%) of material melting at 100-101°. Nandi[33] prepared this ketone by the same method to give a product melting at 98°. The yield based on the ethyl 3-quinolinecarboxylate was 35%.

Bromomethyl 3-Quinolyl Ketone. In accordance with the method described by Nandi,[33] 8 g. (0.04 mole) of methyl 3-quinolyl ketone in 35 ml. of 48% hydrobromic acid was brominated with 7.2 g. (0.04 mole) of bromine vapors. The bromine was passed into the solution at 70-75° with a slow stream of warm air. After all of the bromine had disappeared, the solution was cooled to give 14 g. (93%) of bromomethyl 3-quinolyl ketone hydrobromide melting at 214-216°.

6-Methoxy-8-quinolylaminomethyl 3-Quinolyl Ketone. Ten grams (0.03 mole) of bromomethyl 3-quinolyl ketone hydrobromide and 16 g. (0.09 mole) of 6-methoxy-8-aminoquinoline in 100 ml. of benzene was refluxed for four hours. The mixture was filtered hot, and on cooling 5 g. (29%) of product precipitated from the benzene solution. Two recrystallizations from benzene-petroleum ether (b. p., 60-68°) gave a product melting at 268-269°.

Anal. Calcd. for $C_{21}H_{17}O_2N_3$: N, 12.25. Found: N, 12.40.

Sodamide and 3-Bromoquinoline. Thirty grams (0.15 mole) of 3-bromoquinoline was added very slowly to 0.2 mole of sodamide freshly prepared in 400 ml. of liquid ammonia using 0.3 g. of ferric nitrate as a catalyst. There was a color change from yellow to dark red during the course of the reaction. The ammonia solution was stirred for fifteen minutes after the addition of the bromide was complete. The excess sodamide was destroyed by the addition of solid ammonium chloride. The ammonia evaporated, and the residue was treated with dilute basic solution and extracted with ether. After drying, the material was distilled to give almost a quantitative recovery of starting 3-bromoquinoline.

3-Aminoquinoline. In a 600 ml. beaker, was placed 100 g. (0.48 mole) of 3-bromoquinoline, 250 ml. of concentrated ammonium hydroxide, and 10 g. of copper sulfate. This beaker was placed in a steel bomb and heated at 190° for eighteen hours. The material was cooled and extracted with ether. The product was dried and distilled to remove the solvent. The residue crystallized to a solid which gave, after one recrystallization from toluene, 35 g. (25%) of 3-aminoquinoline melting at 82-83°.

3-Aminoquinoline has been described by Jansen and Wibaut.[32]

γ-Diethylaminopropyl Phenyl Ether. In accordance with a method described by Marvel and co-workers,[34] 485 g. (2.26 moles) of γ-bromopropyl phenyl ether was added slowly over a period of two hours to 350 g. (4.8 moles) of diethylamine. The reaction was carried out at the reflux temperature with vigorous stirring. The mixture was refluxed fourteen hours after the addition was complete. This suspension was extracted with ether, and the solid diethylamine hydrochloride was washed with 500 ml. of ether. The ether solutions were combined, and the solvent was removed. The residue was distilled at reduced pressure to give 416 g. (89%) of material boiling at 104-106°/1.0 mm.

γ-Diethylaminopropyl Bromide Hydrobromide. In a three-necked 2 l. flask fitted with a distillation head and a dropping funnel, was placed 416 g. (2.1 moles) of γ-diethylaminopropyl phenyl ether and 550 ml. of 40% hydrobromic acid. The solution was heated fifteen hours with an oil bath at a temperature sufficient to maintain a slow distillation. During that period 1250 ml. of 40% hydrobromic acid was added dropwise. A mixture of phenol and hydrobromic acid was distilled from the reaction during the heating period. Toward the end of the period of addition, phenol no longer distilled with the hydrobromic acid. The residue was dissolved in 700 ml. of water, and this solution was treated with Norite and filtered. The clear solution was distilled at reduced pressure from a steam bath to remove all of the water. This residue was recrystallized from n-butanol and absolute ether to give a compound melting at 88-91°. The yield of the product was 345 g. (61%). Marvel and co-workers[34] described this method, and they obtained an 80% yield of crude product.

3-(γ-Diethylaminopropylamino)-quinoline. A mixture of 6 g. (0.04 mole) of 3-aminoquinoline and 10 g. (0.053 mole) of γ-diethylaminopropyl

34. Marvel and co-workers, J. Am. Chem. Soc., 49, 2301 (1927).

chloride hydrochloride was heated in an oil bath at 125-135° for one and one-half hours. The reaction mixture was dissolved in dilute hydrochloric acid and filtered. The base was precipitated from the filtrate with ammonium hydroxide, and this product was extracted with ether. After drying the ethereal solution with anhydrous sodium sulfate, the product was distilled to give 2 g. (20%) of material boiling at 160-195°/0.5 mm.

Anal. Calcd. for $C_{16}H_{23}N_3$: N, 16.34. Found: N, 16.29.

5-(γ-Diethylaminopropylamino)-8-methylquinoline. Five grams (0.032 mole) of 5-amino-8-methylquinoline and 10 g. (0.05 mole) of γ-diethylaminopropyl bromide hydrobromide was placed in a 50 ml. Erlenmeyer flask. This mixture, under an atmosphere of dry nitrogen, was heated in an oil bath at 140-150° for two and one-half hours. The melt was dissolved in water and filtered. The free base was precipitated from the clear solution by the addition of ammonium hydroxide solution, and the material that separated was largely the starting quinoline compound. After isolating this material, 5 g. (0.025 mole) of γ-diethylaminopropyl bromide hydrobromide was added, and this mixture was heated in the oil bath at 140-160° for eight hours. The reaction melt was not readily soluble in water, and a few drops of concentrated hydrochloric acid were added. The acid solution was filtered, and then the product was precipitated with concentrated ammonium hydroxide. The oily material was extracted with several portions of ether, and this solution was dried over anhydrous sodium sulfate. The solvent was removed by distillation from a steam bath. The crude product was distilled at reduced pressure to give 2.5 g. (30%) of material boiling at 175-195°/1.0 mm.

Anal. Calcd. for $C_{17}H_{25}N_3$: N, 15.55. Found: N, 15.26.

The 5-amino-8-methylquinoline used in this experiment was supplied by S. M. Spatz.[29] He obtained this compound by nitrating 8-methylquinoline and then reducing it to the corresponding amino compound.

5-(γ-Diethylaminopropylamino)-6-methylquinoline. The 5-amino-6-methylquinoline used in this experiment was prepared by Spatz[29] in a manner similar to the preparation of its isomer as described above.

Eight grams (0.05 mole) of 5-amino-6-methylquinoline and 15 g. (0.08 mole) of γ-diethylaminopropyl chloride hydrochloride was heated in an oil bath at 110° for four hours. The bath temperature was raised to 140° for three hours. The reaction product was completely dissolved in water. Ammonium hydroxide was added to the aqueous solution to precipitate the amine. This product was distilled, subsequent to extraction and drying, to give 2.9 g. (22%) of a light yellow oil boiling at 160-170°/1.0 mm.

Anal. Calcd. for $C_{17}H_{25}N_3$: N, 15.55. Found: N, 15.65.

3-(γ-Diethylaminopropylamino)-9-ethylcarbazole. Eight grams (0.04 mole) of 3-amino-9-ethylcarbazole and 15 g. (0.08 mole) of γ-diethylaminopropyl chloride was heated four and one-half hours in an oil bath. Over this heating period the temperature was slowly increased from 120° to 150°. The reaction mixture was dissolved in dilute hydrochloric acid to give a clear red solution. After cooling, the solution was neutralized with ammonium hydroxide. The free base was extracted with several portions of ether, and the ethereal solution was washed with water. After drying over anhydrous sodium sulfate, the solvent and a small portion of low-boiling material was removed at reduced pressure. The product was distilled to give 8.5 g. (66%) of a transparent light brown liquid boiling at 260-265°/1.0 mm.

Anal. Calcd. for $C_{21}H_{29}N_3$: N, 13.00. Found: N, 13.12.

1-Aniline-2,5-dimethylpyrrole. This pyrrole has been described briefly by Knorr.[35] Nobis prepared this compound by condensing acetonylacetone and phenylhydrazine without solvent to give a 7% yield of the product.[36]

In accordance with the general procedure described by Knorr, to 50 ml. of glacial acetic acid was added 10.8 g. (0.1 mole) of phenylhydrazine and 11.4 g. (0.1 mole) of acetonylacetone. This solution was heated on a steam bath for one and one-half hours. After cooling, the reaction mixture was neutralized with sodium carbonate and steam distilled. This distillation was rather slow, so the organic material was extracted with ether and dried. This crude product was distilled at 1.0 mm. pressure to give 4.5 g. (24%) of material boiling at 132-140°. This solid was recrystallized from 50% methanol to give material melting at 92-93°.

p-Chlorophenylhydrazine. This compound was prepared in accordance with the method described by Willgerodt and Böhm.[37] One hundred and thirty-five grams (1.05 moles) of p-chloroaniline was diazotized at 0° using 2000 ml. of 25% hydrochloric acid at 85 g. (1.2 moles) of sodium nitrite in 500 ml. of water. Four hundred and seventy-five grams of stannous chloride ($SnCl_2.2H_2O$) in 500 ml. of concentrated hydrochloric acid was added very slowly to this diazonium solution at 0° with vigorous stirring. The bulky precipitate which separated was filtered and washed with dilute hydrochloric acid. This solid was suspended in water, and with efficient stirring, sodium hydroxide solution was added until the mixture was basic. The first solid material dissolved, and

35. Knorr, Ber., 22, 170 (1889).

36. Unpublished studies by J. F. Nobis.

37. Willgerodt and Böhm, J. prakt. Chem., 43, 482 (1891).

another precipitate separated as the base was added. The solid was filtered and dried to give 65 g. (44%) of crude product. Recrystallization from petroleum ether (b. p., 80-110°) gave material melting at 83-85°.

A second preparation, using similar conditions, gave the same yield of a product melting at 86-87°. In this experiment, the addition of the base to the complex tin salt was much slower and the stirring during this addition was more efficient.

1-(p-Chloroanilino)-2,5-dimethylpyrrole. Seven grams (0.05 mole) of p-chlorophenylhydrazine and 5.7 g. (0.05 mole) of acetonylacetone dissolved in 50 ml. of glacial acetic acid was refluxed for three hours. This solution was poured into ice water and neutralized with sodium carbonate. The crude product was extracted with ether and dried over anhydrous sodium sulfate. This material was distilled at reduced pressure to give 5 g. (46%) of colorless oil boiling at 145-155°/1.0 mm. This oil rapidly became colored and later solidified. Crystallization from aqueous methanol gave light red crystals melting at 88-89°. A mixed melting point with the starting material was depressed.

Anal. Calcd. for $C_{12}H_{13}N_2Cl$: N, 12.78. Found: N, 13.00.

γ-Diethylaminopropyl Chloride Hydrochloride and Carbazole. Ten grams (0.054 mole) of γ-diethylaminopropyl chloride hydrochloride and 7.5 g. (0.044 mole) of carbazole was sealed in a tube. The tube was heated in an oven at 200° for three hours. After opening the tube, an attempt to dissolve the reaction mixture in hot dilute hydrochloric acid failed. Extraction of the melt with hot ethanol left a solid which was identified as unreacted carbazole.

The 9-carbazyllithium was prepared by the addition of 40 g. (0.24 mole) of carbazole to a solution containing 0.24 mole of methyllithium. The

solid powdered carbazole was added to the ether solution of methyllithium. Color test I[21] was negative and some unreacted carbazole remained suspended in the ether after the addition of all the carbazole was complete. To this suspension was added dropwise the ether solution obtained from extracting the oil that resulted from the neutralization of 50 g. (0.3 mole) of γ-diethylaminopropyl chloride hydrochloride. The ether solution of the chloride was dried well over anhydrous sodium sulfate before the addition to the reaction mixture. The addition of the chloride resulted in the formation of a precipitate. The ether suspension was stirred for forty minutes after all of the chloride was added, and then the mixture was hydrolyzed by the addition of water. The mixture was filtered to give 25 g. (64%) of unreacted carbazole. The ether layer was separated, and this solution was extracted with a dilute hydrochloric acid solution. Neutralization of this acid extract gave a very small amount of oil which was not identified. More carbazole was recovered from the ether extract so that only very little of the total carbazole was not recovered.

IV. DISCUSSION

1. Testing of Antimalarial Compounds

The physiological tests on possible antimalarial compounds are carried out by first giving a screening test on all drugs. These preliminary tests are carried out on birds infected with avian malaria. The birds used in these biological tests are generally canaries, young chicks, or ducklings. If the preliminary tests indicate outstanding activity, the drug is tested on other animals, and later clinical tests are made. The results obtained on further testing often prove that the preliminary tests have not been an accurate measure of the value of a given drug as an antimalarial agent. Two reasons why this discrepancy occurs are: first, the variations and inaccuracies of biological testing; and second, the fact that the activity of a given compound against avian malaria is not the same against human malaria. This latter factor is a fundamental weakness in the testing procedure, but testing for avian malaria is the best single criterion known for the evaluation of pharmacological action without actually testing on man.

The physiological assay is designed to test both the prophylactic and the therapeutic value of the drugs. The prophylactic tests are carried out by feeding the drug and later infecting the bird with the malarial parasite. With the therapeutic tests, the birds are infected before the drug is administered. For the most part, the tested drugs have been shown to have therapeutic rather than prophylactic value.

The compounds prepared in this investigation were all made either as antimalarial compounds or intermediates in the synthesis of possible

antimalarial agents. The compounds that were tested have been sent to Parke-Davis Company of Detroit, Michigan, who have relayed them to cooperating laboratories for pharmacological testing under the auspices of the United States Government. These cooperative research groups have aided this investigation by sending the results of the physiological tests back to our laboratories. This information is sent in order to assist in the development of better antimalarial compounds, and the United States Government has restricted the publication of specific results about these pharmacological tests. Therefore, the information can not be included in this discussion.

2. Synthesis of Antimalarial Compounds

Sulfur Derivatives

The typical basic side-chain found in most effective synthetic antimalarials is the dialkylaminoalkylamino group (VII). The diethyl-

$$R_2N(CH_2)_nN(H)-$$

(VII)

amino group has been observed to be one of the best terminal groups used in these basic side-chains. In this investigation, variations in this typical side-chain were effected by the interruption of the carbon chain between the two nitrogen atoms by a sulfide group. This type can be illustrated by a general group called (dialkylaminoalkylmercapto)-alkylamino (VIII).

$$R_2N(CH_2)_nS(CH_2)_mN(H)-$$

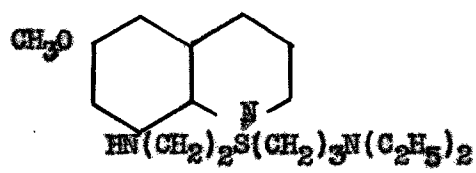
(VIII)

The chloro compounds that were prepared to give this type of side-chain are as follows: (1) γ-diethylaminopropyl γ-chloropropyl sulfide (n = 3, m = 3), (2) β-diethylaminoethyl γ-chloropropyl sulfide (n = 2, m = 3), and (3) γ-diethylaminopropyl β-chloroethyl sulfide (n = 3, m = 2). These chlorosulfides were prepared by the general reactions illustrated below.

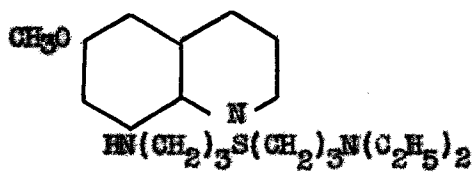
$$(C_2H_5)_2N(CH_2)_nCl + NaS(CH_2)_mOH \longrightarrow (C_2H_5)_2N(CH_2)_nS(CH_2)_mOH$$

$$(C_2H_5)_2N(CH_2)_nS(CH_2)_mOH \xrightarrow{SOCl_2} (C_2H_5)_2N(CH_2)_nS(CH_2)_mCl$$

Two of the aliphatic chloro compounds were condensed with 6-methoxy-8-aminoquinoline (plasmoquin base),[38] which has been established as an exceptionally good aromatic nucleus for antimalarial compounds. The two quinoline compounds prepared were 8-[β-(γ-diethylaminopropylmercapto)-ethylamino]-6-methoxyquinoline (IX) and 8-[γ-(γ'-diethylaminopropylmercapto)-propylamino]-6-methoxyquinoline (X).



(IX)



(X)

38. The 6-methoxy-8-aminoquinoline and the 6,9-dichloro-2-methoxy-acridine were kindly supplied by Parke-Davis Company of Detroit, Michigan.

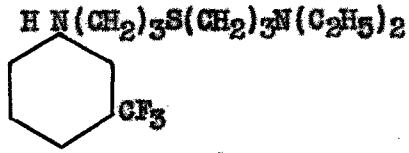
These compounds can be compared with plasmoquin which has been tested sufficiently to definitely establish its antimalarial activity. A comparison of this type can give rise to general conclusions about the change in activity by the variation in the basic side-chain.

Since the variation in the length of a carbon chain has often changed the activity to a considerable degree, the α-chloromethyl β-diethylaminoethyl sulfide and 6-methoxy-8-aminoquinoline would react to give an interesting member of this series. The attempt to prepare this α-chloromethyl derivative failed, but the only method tried was the attempted preparation of α-chloromethyl β-diethylaminoethyl sulfide. Another interesting compound that could be prepared in this series is the product obtained from the condensation of δ-chlorobutyl β-diethylaminoethyl sulfide and 6-methoxy-8-aminoquinoline. The δ-chlorobutyl β-diethylaminoethyl sulfide could be prepared in a manner similar to the lower homolog. δ-Diethylaminobutyl chloride could be prepared from tetramethylene chlorohydrin, and diethylamine by the following reactions:

$$Cl(CH_2)_4OH \xrightarrow{(C_2H_5)_2NH} (C_2H_5)_2N(CH_2)_4OH$$

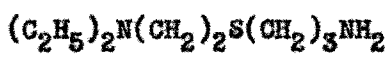
$$(C_2H_5)_2N(CH_2)_4OH \xrightarrow{SOCl_2} (C_2H_5)_2N(CH_2)_4Cl$$

In order to observe the effect of these sulfur-containing basic side-chains attached to a nucleus that has no particular antimalarial activity, m-trifluoromethylaniline was condensed with γ-diethylaminopropyl γ-chloropropyl sulfide to give 3-[γ-(γ'-diethylaminopropylmercapto)-propylamino]-trifluoromethylbenzene (XI).



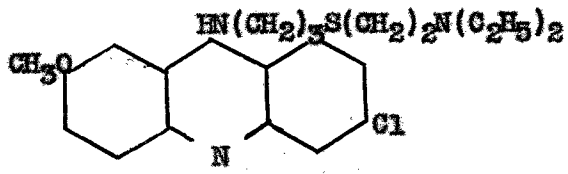
(XI)

The best available method for the introduction of the typical side-chain into the 9-position of acridine is the condensation of an aliphatic amine with the 9-chloroacridine derivative. The β-diethylaminoethyl γ-aminopropyl sulfide (XII) was prepared from sodium β-diethylaminoethyl mercaptide and γ-bromopropylphthalimide by the Gabriel synthesis. This



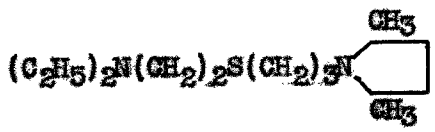
(XII)

amino side-chain was condensed with 6,9-dichloro-2-methoxyacridine[38] to give 9-[γ-(β-diethylaminoethylmercapto)-propylamino]-6-chloro-2-methoxyacridine (XIII).



(XIII)

The reaction of β-diethylaminoethyl γ-aminopropyl sulfide with acetonylacetone gave γ-(2,5-dimethyl-1-pyrryl)-propyl β-diethylaminoethyl sulfide (XIV), which is a very interesting compound since it



(XIV)

contains the 2,5-dimethyl-1-pyrryl group. This group has shown some

antimalarial value.

The synthesis of some of the materials used above required β-diethylaminoethyl mercaptan. Prior to this investigation, the mercaptan was not readily available. Gilman and Woods[10] describe the preparation of this mercaptan from ethylene sulfide and lithium diethylamide, but these starting materials are not easily obtained. The preparation of the mercaptan from β-diethylaminoethyl chloride and sodium hydrosulfide[17] is a more practical method of preparation, since the starting materials are easily available. Since the completion of this investigation, Albertson and Clinton[18] have described the synthesis of β-diethylaminoethyl mercaptan from β-diethylaminoethyl chloride hydrochloride and thiourea in an excellent yield. The latter method is undoubtedly the best procedure for the preparation of this mercaptan at the present time. Gilman and Woods[10] report the reaction of β-diethylaminoethyl chloride and thiourea. The low yield obtained by these workers probably can be explained by the use of the free base of the chloride rather than the hydrochloride.

The secondary carbinol group has been shown to be an effective functional group in enhancing antimalarial activity. The introduction of a carbinol group into some of these typical sulfur-containing side-chains was approached by reacting epichlorohydrin and sodium β-diethylaminoethyl mercaptide to give 1-diethylaminoethylmercapto-2,3-epoxypropane (XV). This epoxy compound was treated with diethylamine in an

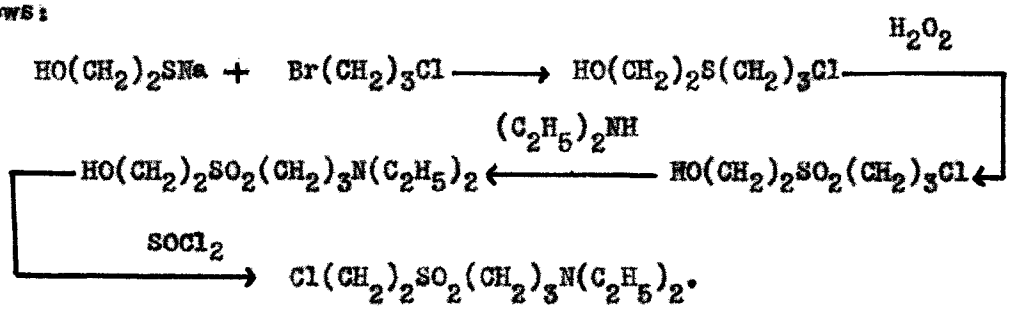
$$(C_2H_5)_2N(CH_2)_2SCH_2\underset{\diagdown\,O\,\diagup}{CH}CH_2$$

(XV)

effort to open the cyclic ether group to give a secondary carbinol. Since the secondary amine failed to react with the epoxy group, this

compound was treated with 8-(N-lithio)-amino-6-methoxyquinoline, but only unchanged starting material was recovered. Because the cleavage of the ether failed with both diethylamine and the lithium amide, the structure of the compound was questioned. Fractionation from a modified Claisen flask several times gave the same product. Gilman and Woods[10] first prepared and analyzed the compound for nitrogen. This compound reacts with hydrochloric acid to give a mixture of higher boiling products; thus indicating the presence of the epoxy group. The boiling point is lower than that expected for any possible product obtainable from epichlorohydrin and the sodium diethylaminoethyl mercaptide. From all of these factors, this compound was assumed to be the 1-diethylaminoethylmercapto-2,3-epoxypropane. The reaction of this compound with a secondary amine might be started or catalyzed with a small amount of water or some other material that attacks the ether linkage. All of the possibilities were not explored in this investigation.

Most of the sulfur compounds prepared were sulfides, but an effort was made to prepare some of the corresponding sulfones. By oxidizing the sulfide before the introduction of an amino group, less difficulty was expected. The general synthesis proposed can be illustrated as follows:

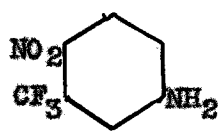


β-Hydroxyethyl γ-chloropropyl sulfide was prepared in good yield from the readily available sodium β-hydroxyethyl mercaptide and γ-chloropropyl

bromide. The oxidation of this sulfide and of the corresponding acetoxy derivative failed to give a product which could be purified. Other methods of preparing these sulfones were not attempted. In connection with this particular work, a publication appeared recently by Clinton and co-workers[20] in which β-diethylaminoethyl γ-chloropropyl sulfide was oxidized to the sulfone in 42% yield. This oxidation was carried out with 30% hydrogen peroxide. These workers could not purify their product, but a picrate was prepared and analyzed.

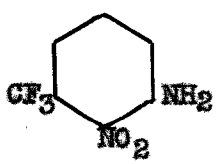
Trifluoromethyl Derivatives

m-Trifluoromethyl acetanilide was nitrated by two methods to give the three isomers. The nitration was carried out by the methods described by Rouche.[24] The first method, nitration in sulfuric acid, gave 43% of 3-trifluoromethyl-4-nitroaniline (XVI) and a mixture of other isomers. The second nitration with acetyl nitrate gave 20% of the

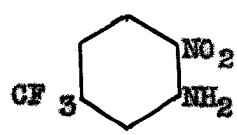


(XVI)

3-trifluoromethyl-2-nitroaniline (XVII) and 17% of 3-trifluoromethyl-6-nitroaniline (XVIII).



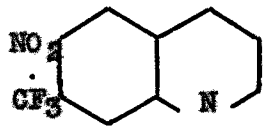
(XVII)



(XVIII)

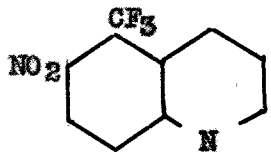
These nitrated m-trifluoromethylaniline derivatives were each reacted with glycerol and arsenic acid in the Skraup synthesis. The 3-trifluoromethyl-4-nitroaniline (XVI) gave a good yield of a

7-trifluoromethyl-6-nitroquinoline (XIX). There was no 5-trifluoro-



(XIX)

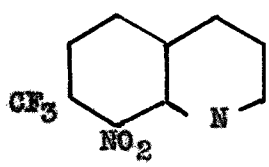
methyl-6-nitroquinoline (XX) isolated from this ring closure. The



(XX)

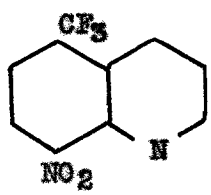
structure of the 7,6-isomer was established by reducing the nitro compound to the amine and deaminating to give 7-trifluoromethylquinoline. The 7-trifluoromethylquinoline was compared with an authentic specimen prepared by the Skraup reaction with m-trifluoromethylaniline. The structure of the 7-trifluoromethylquinoline was previously established by Gilman and Blume[11] by the hydrolysis of the trifluoromethyl group to the carboxylic acid.

An attempt to prepare 7-trifluoromethyl-8-nitroquinoline (XXI) from



(XXI)

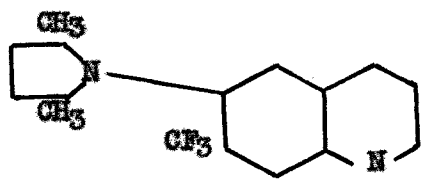
3-trifluoromethyl-2-nitroaniline by the Skraup synthesis gave an unidentified material. The preparation of the 5-trifluoromethyl-8-quinoline (XXII) also failed to give a definite product.



(XXII)

These Skraup reactions were tried only once, and these failures were probably the result of temperature control.

The 7-trifluoromethyl-6-nitroquinoline was reduced with stannous chloride in good yield to the corresponding amine. This amine was condensed with acetonylacetone to give 7-trifluoromethyl-6-(2,5-dimethyl-1-pyrryl)-quinoline (XXIII). -Diethylaminopropyl chloride hydrochloride

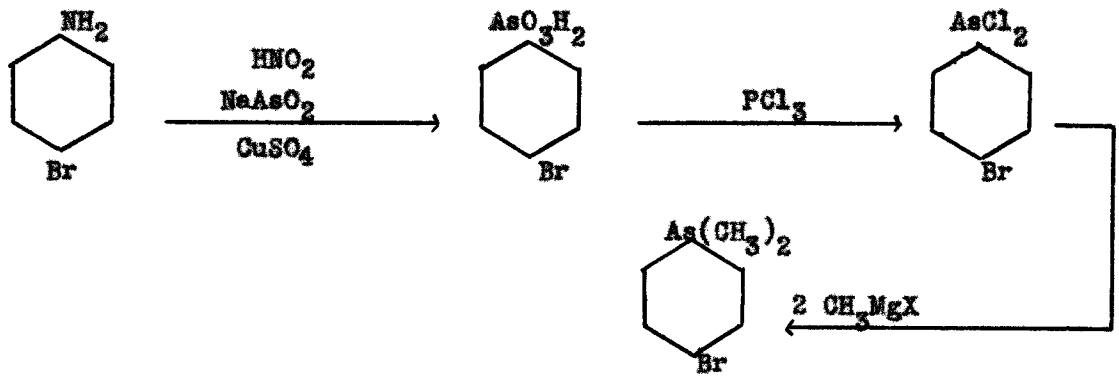


(XXIII)

and the 7-trifluoromethylquinoline failed to give a product until the mixture was heated for forty-eight hours at a relatively high temperature. The product obtained using these severe conditions could not be purified to give a correct nitrogen analysis. A picrate prepared from this impure product was purified and this derivative analyzed correctly for nitrogen. An attempt to condense this same amine with γ-diethylaminopropyl γ-chloropropyl sulfide gave only starting material after long periods of heating. This 7-trifluoromethyl-6-aminoquinoline was unusually resistant to condensation with aliphatic chloro compounds, even though the reaction with acetonylacetone proceeded normally.

Arsine Derivatives

The arsine derivatives prepared in this investigation were all synthesized from p-bromophenyldimethylarsine, which was prepared by the following series of reactions:

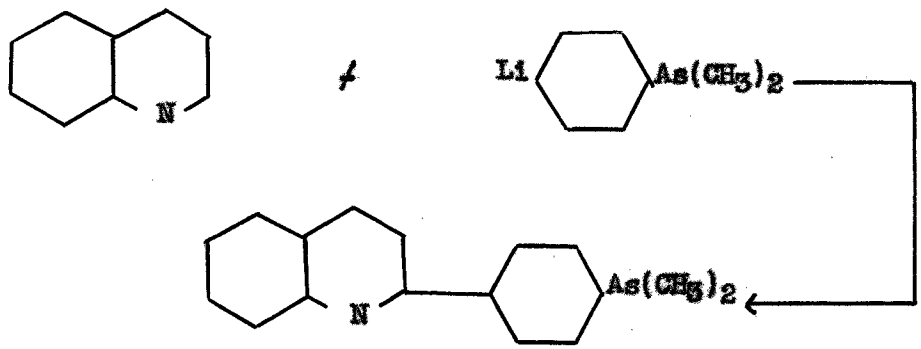


The conversion of p-bromoaniline to the corresponding arsonic acid by the Bart reaction was carried out in large quantities by a modified method of Blicke and Webster.[25] The conversion of the arsonic acid to the dichloroarsine was carried out by the use of phosphorus trichloride in acetic acid. This reaction proceeded very well, and this method appeared to be better than the method using hydrogen iodide and sulfur dioxide.

p-Bromophenyldimethylarsine has previously been prepared by the reaction of p-bromophenylmagnesium bromide and dimethyliodoarsine. The reaction of methylmagnesium iodide and p-bromophenyldichloroarsine gave a good yield of the dimethyl derivative. This latter procedure is the better method since the starting materials are more accessible.

p-Bromophenyldimethylarsine reacts readily with lithium metal to give p-lithiophenyldimethylarsine. This bromide does not react so readily with magnesium, but the Grignard reagent will form by refluxing the mixture of magnesium in the ether solution of the bromide.

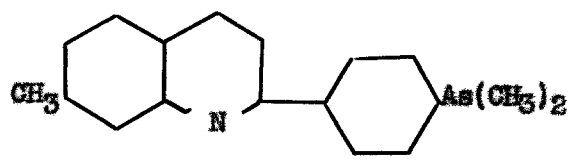
A series of quinoline derivatives was treated with p-lithiophenyldimethylarsine to give the corresponding dimethyl-p-(2-quinolylphenyl)-arsine compounds as illustrated below by the reaction with quinoline:



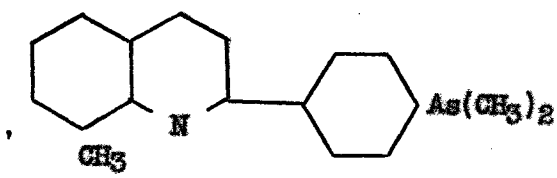
(XXIV)

In the preparation of these 2-phenylquinoline derivatives, the 1,2-dihydroquinoline was first formed, and the oxidation of this form with nitrobenzene was necessary. The dimethyl-p-(1,2-dihydro-2-quinolylphenyl)-arsine was isolated and distilled.

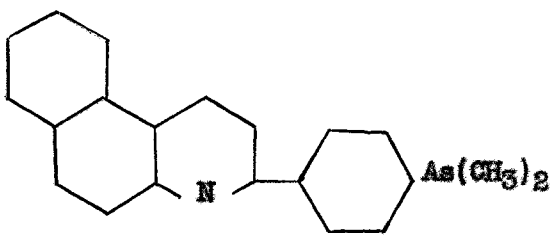
The compounds prepared by the anil addition reaction with p-lithiophenyldimethylarsine were: dimethyl-p-(2-quinolylphenyl)-arsine (XXIV), dimethyl-p-(7-methyl-2-quinolylphenyl)-arsine (XXV), dimethyl-p-(8-methyl-2-quinolylphenyl)-arsine (XXVI), dimethyl-p-(5,6-benzo-2-quinolylphenyl)-arsine (XXVII), dimethyl-p-(6-chloro-2-quinolylphenyl)-arsine (XXVIII), and dimethyl-p-(2-pyridylphenyl)-arsine (XXIX).



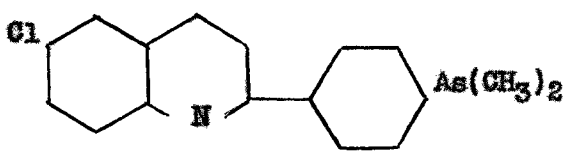
(XXV)



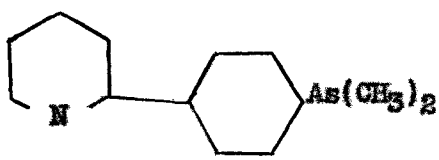
(XXVI)



(XXVII)

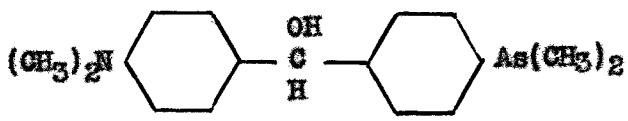


(XXVIII)



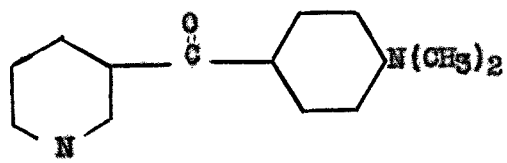
(XXIX)

The reaction of p-dimethylaminobenzaldehyde with p-dimethylarsinophenylmagnesium bromide gave p-dimethylaminophenyl-p'-dimethylaminoarsinocarbinol (XXX). In a similar preparation, p-lithiophenyldimethyl-



(XXX)

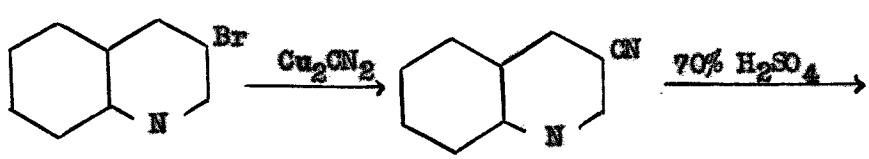
arsine was added to 3-cyanoquinoline, but no pure product could be isolated from this reaction. p-Dimethylaminophenyllithium and 3-cyanoquinoline gave the expected product (p-dimethylaminophenyl 3-quinolyl ketone) (XXXI) in 26% yield.

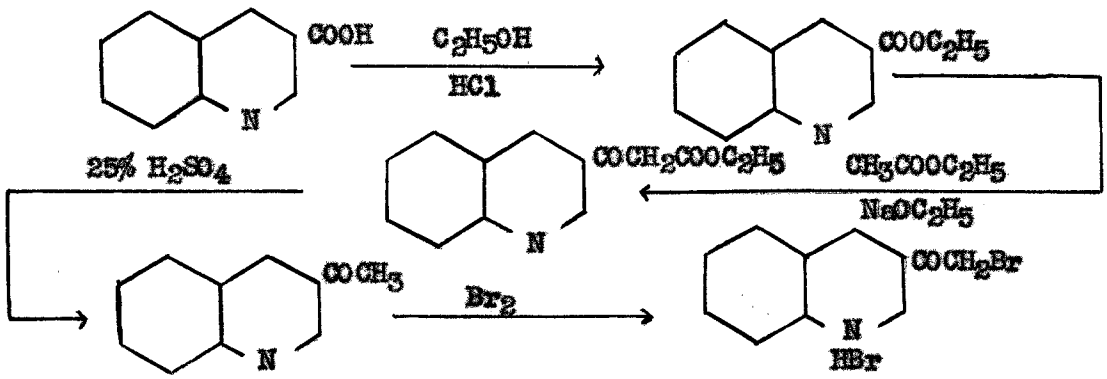


(XXXI)

Miscellaneous Amines

Spatz[29] developed the preparation of 3-bromoquinoline so that this material could be obtained in rather large quantities. From the 3-bromoquinoline, a number of 3-substituted quinoline compounds was prepared. Bromomethyl 3-quinolyl ketone was prepared by the following reactions:

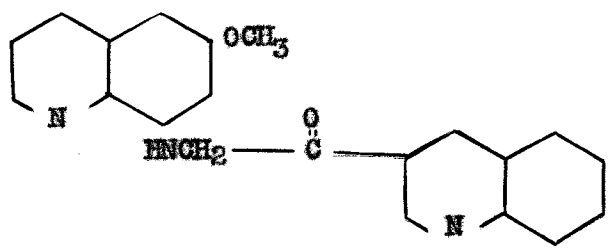




The yield of ethyl 3-quinolinecarboxylate from the acid was improved considerably by the use of dry hydrogen chloride and absolute ethanol. Previously the esterification was carried out by Spatz[31] who used sulfuric acid and absolute ethanol. Attempts to prepare this ester directly from the 3-cyanoquinoline using absolute ethanol and dry hydrogen chloride gave the imido ether.

Nandi[33] described the preparation of bromomethyl 3-quinolyl ketone by the method used in this investigation. The β-keto ester was not purified and described by Nandi, and the yield of the methyl ketone, based on the starting ethyl 3-quinolinecarboxylate was only 35%. In this investigation, the method used by Nandi was modified to give a yield of 73%. The bromination of the methyl 3-quinolyl ketone in hydrobromic acid gives an excellent yield of the bromomethyl derivative.

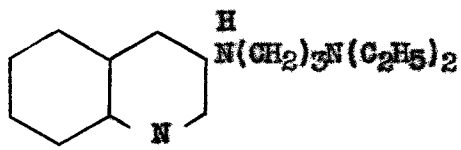
Bromomethyl 3-quinolyl ketone hydrobromide was reacted with 6-methoxy-8-aminoquinoline to give a low yield of 6-methoxy-8-quinolylaminomethyl 3-quinolyl ketone (XXXII).



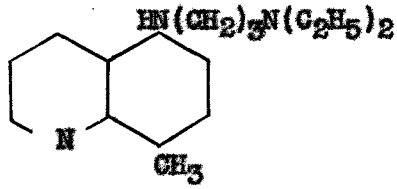
(XXXII)

Prior to this research, a quinoline containing the typical basic side-chain in the 3-position had not been prepared. The preparation of 3-aminoquinoline from the readily available 3-bromoquinoline has been made. The 3-bromoquinoline was added to sodamide, freshly prepared in liquid ammonia. Reaction with the bromo compound did not occur at the temperature of liquid ammonia. Perhaps at a higher temperature, the reaction would take place, but sodamide also reacts with the anil linkage at higher temperatures. Rather than attempt the reaction with sodamide at higher temperatures, the 3-bromoquinoline and concentrated ammonium hydroxide using copper sulfate as a catalyst was placed in a steel bomb at 190°. At this temperature and pressure, a 25% yield of the 3-aminoquinoline was obtained. This reaction had previously been carried out by Jansen and Wibaut[32] with a very small amount of 3-bromoquinoline in a sealed tube.

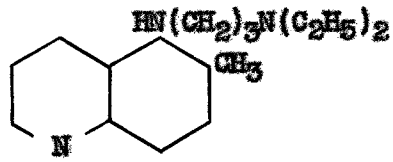
Three aminoquinolines were condensed with γ-diethylaminopropyl bromide hydrobromide to give new quinoline compounds containing the typical basic side-chain. The three compounds prepared were: 3-(γ-diethylaminopropylamino)-quinoline (XXXIII), 5-(γ-diethylaminopropylamino)-8-methylquinoline (XXXIV), and 5-(γ-diethylaminopropylamino)-6-methyl-quinoline (XXXV).



(XXXIII)

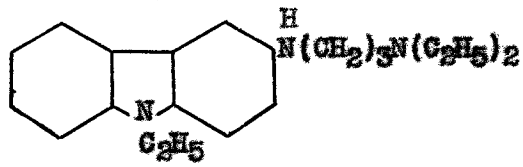


(XXXIV)



(XXXV)

Closely related to these compounds, the 3-(γ-diethylaminopropylamino)-9-ethylcarbazole was prepared by a similar condensation (XXXVI).



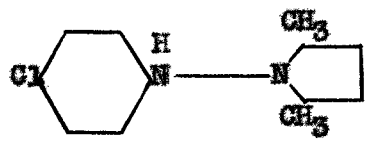
(XXXVI)

An attempt to condense γ-diethylaminopropyl chloride hydrochloride with carbazole failed to give a reaction. In an attempt to obtain this compound by another method, 9-carbazyllithium was treated with γ-diethylaminopropyl chloride. Both of these reactions failed to give the product. The product could probably be prepared by a more indirect method. One method which might be used to prepare the 9-(γ-diethylaminopropyl)-carbazole is the reaction of γ-chloropropyl p-toluenesulfonate with either carbazole or 9-carbazyllithium to give 9-(γ-chloropropyl)-carbazole. This chloro derivative would react with diethylamine to give the desired product. In connection with the studies of compounds containing the 2,5-dimethyl-1-pyrryl group, acetonylacetone was condensed

with phenylhydrazine and p-chlorophenylhydrazine to give the corresponding pyrryl derivatives.

The condensation of phenylhydrazine and acetonylacetone was carried out by a modified method of Knorr[35] to give a 24% yield of the product. These condensations with the phenylhydrazine compounds proceed in much better yield when acetic acid is used for the solvent. Similar reactions with aromatic amines are carried out without solvent or in absolute ethanol.

p-Chlorophenylhydrazine was prepared from p-chloroaniline by the reduction of the diazonium salt with stannous chloride.[37] The condensation of the p-chlorophenylhydrazine with acetonylacetone gave a 46% yield of 1-(p-chloroanilino)-2,5-dimethylpyrrole (XXXVII).



(XXXVII)

V. SUMMARY

1. Some of the theoretical aspects of synthetic antimalarials have been discussed.

2. Series of each of the following types of compounds have been prepared for antimalarial testing: aromatic compounds with sulfur-containing basic side-chains, trifluoromethyl derivatives, arsine derivatives, miscellaneous quinoline compounds containing basic side-chains, and some 2,5-dimethyl-1-pyrryl derivatives.

3. The results of the pharmacological tests, which were carried out under the auspices of the United States Government, are restricted. Accordingly, publication of such results must wait on future release.