SYNTHETIC ANTIMALARIALS

PART I. PHENOTHIAZINE DERIVATIVES

PART II. DIPHENYLAMINE DERIVATIVES

PART III. ETHANOLAMINE DERIVATIVES

By

Leon Goldman

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

1944

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

ACKNOWLEDGMENT

The writer wishes to express his appreciation to Dr. Nathan L. Drake for the suggestion of this problem and for his counsel and continuous interest during the course of the research.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF PLATES

HISTORICAL INTRODUCTION

General Discussion

Of the protozoan diseases which are known, malaria is probably the most destructive and widespread in man. Every year it brings great suffering to many millions of people; in India alone there are an estimated one hundred million cases and one million deaths per year from malaria (397). Although it is primarily a disease of the tropics, it attacks in every zone; there are four million cases and four thousand deaths per year in the southern United States alone (398). The Canal Zone and our insular possessions are heavily infected by this disease (51). Malaria has been recognized since ancient times and has had a very powerful influence on the progress of civilization. During peaceful world conditions the fight against malaria costs many millions of dollars yearly and is of prime economic importance, but during wars its influence is multiplied many times. In areas infected with malaria, battles may often be decided by which side has the greatest protection against the disease. Reports issuing from the present war indicate that this very thing has already occurred.

Although the nature and transmission of malaria has been understood since only about sixty years ago, the value of cinchona bark in relieving this disease was known to the Peruvian Indians for many centuries and as early as 1630 was used in Europe in the treatment of malaria (150). The cinchona tree was originally native to the mountain sides of the South American Cordilleras, where it grew in regions twelve hundred to thirty-five hundred meters above sea level in Caracas, Bolivia, New Granada, Ecuador and Peru. At present it is cultivated

very successfully in other countries such as Java, Batavia, the Indies, Ceylon and in some other places (989). The name Cinchona was given by Linné to the species of quinine-producing trees in memory of the Countess of Chinchon, the wife of the Viceroy to Peru, who, as the legend has it, was stricken with malaria in the city of Lima in 1638 (98). The Spanish governor of the neighboring town of Loxa supplied some powdered bark which amazingly caused her immediate recovery. When the Countess returned to Spain she supplied her physician with quantities of the bark for curing persons on the Chinchon estates in Southern Spain. By 1640, according to the story, the use of the drug had spread over all of Europe. This story of the introduction of cinchona bark has been disproved by the discovery of the diary of the Count of Chinchon in which a more correct account of the history of cinchona is given (989). At the end of the sixteenth century and beginning of the seventeenth century there was a considerable export of medicinals from the New World to Europe. One of the products was the bark of a tree from which was obtained Peruvian balsam, used as a febrifuge. The suppliers were not able to meet the demand for the drug, so they resorted to adulteration with the bark of a similar tree. This bark, which finally displaced the original, was derived from cinchona trees.

Little advance was made in the treatment of malaria until 1880 when the French army surgeon Laveran in Algiers discovered plasmodia in the blood of a malaria patient. Another great advance was made when Ross and Grassi, in 1898, showed that the anopheline mosquito is necessary for the transmission of the disease.

Malaria is a disease which is produced by plasmodia which are injected into the blood stream of man by certain mosquitoes of the genus

Anopheles. Malaria is characterised by paroxysms of intermittent fever which may occur daily (quotidian fever), every two days (tertian fever) or every four days (quartan fever); or the fever may be continuous. The name Malaria is derived from the Italian "mala aria", meaning "bad air", since the sickness was supposed to be due to poisonous vapors from damp ground.

After Laveran's discovery in 1880 of plasmodia in the blood of a malaria patient, further study was made in Italy by Marchesafava and Celli who, in 1885, published the first careful description of the parasite. In 1894, Sir Patrick Manson suggested that an intermediate host must exist outside of the human body to allow for transmission of the disease. He suggested that this host should be a sucking insect. This suggestion lead to the discovery by Ross and Grassi of the Anopheles mosquito as the link in the chain of the life cycle of the parasite.

The malarial parasites are species of the genus Plasmodium in the family Plasmodiidae in the order Haemosporidia of the sub-class Telosporidia of the class Sporozoa of the sub-phylum Plasmodroma of the phylum Protozoa. The species of the genus Plasmodium which are most important as causative agents of malaria and the hosts which they infest are the following:

Man	Monkeys and Apes	Birds
P. malariae	P. knowlesi	P. praecox
P. falciparum	P. inui	P. relictum
P. vivax	P. cynomolgi	P. cathemerium
P. ovale	P. brasilianum	P. lophurae
P. pleurodyniae	P. koshi	P. danilewskyi
P. tenue	P. pitheci	P. capistrani
	P. reichenowi	

The most important agents as regards human malaria are Plasmodium vivax, P. falciparum and P. malariae. Benign Tertian malaria is caused by

P. vivax; Malignant Tertian, Sub-Tertian, Aestive-Autumnal or Pernicious malaria are caused by P. falciparum; and Quartan malaria is caused by P. malariae.

When a mosquito is infected with malaria it has in its salivary glands many malaria parasites which are in the form of slender spindles having a central nucleus and a length of about ten microns, called sporozoites. When the infected mosquito bites a human victim it injects into the blood stream some saliva which is teeming with sporozoites. These organisms then attack erythrocytes and enter them. While in the erythrocytes the sporozoites grow and change their shape to a ring form about three microns in diameter having a brightly stained eccentrically placed nucleus. At this stage it is called a trophozoite. When fully grown the trophozoite is an asexual form, called a schizont, and undergoes nuclear fission (schizogony). There follows several subsequent nuclear divisions, and the schizont matures into a merocyte. The merocyte fills the greater part of the erythrocyte which has given nourishment to the parasite at the expense of cell substance. The erythrocyte ruptures at this point to liberate into the blood stream from eight to thirty-two young spore-like bodies called merozoites. Also liberated are toxic waste products from the disintegrated red cells. The release of these poisonous substances gives rise to paroxysms of fever characteristic of malaria. The periods of time for this process to occur vary with the infecting organism: twenty-four to forty-eight hours in aestive-autumnal malaria, forty-eight hours in tertian malaria, and seventy-two hours in quartan malaria. The liberated merozoites seek to enter new erythrocytes, but many are destroyed by phagocytosis. Those which escape destruction penetrate erythrocytes, and the cycle is repeated.

A different course in the cycle sometimes occurs when the schizonts or merozoites undergo a metamorphosis and become sexual forms called macro (female) and micro (male) gametocytes. It is the gametocytes which infect mosquitoes, but have no effect on the course of human malaria. When a mosquito bites an infected human it takes into its stomach some of the gametocytes and merozoites. The asexual merozoites soon die, but the macrogametocytes become mature and are called macrogametes. The microgametocytes extrude long slender, whip-like extrusions (flagella) which break off and move about. Eventually they penetrate the macrogametes and the sexual cycle begins (sporogony). The product of fertilization is a zygote which at first is round, but later becomes elongated and becomes a motile oökinete. This form penetrates the stomach wall, encysts, and becomes an oöcyst on the outer surface of the stomach wall. This form grows into a sporont which then undergoes nuclear division into sporoblasts, causing the cyst to rupture, thus releasing several hundred to ten thousand sporozoites from each cyst into the body cavity of the mosquito. The sporozoites migrate into the salivary glands where they await injection into a suitable host in order to continue the life cycle. (See Plate I.)

The fight against malaria has been carried out in two ways: 1. general control and prophylactic measures to prevent infection; 2. therapeutic treatment after infection. The general control measures are concerned with destruction of the mosquito larvae by oiling breeding places and draining ponds, lakes, and swamps; use of insecticides to kill mosquitoes and their larvae; personal precautions against mosquito bites by use of screens, nets, or insect repellents; and avoidance of regions where malaria is prevalent. Chemoprophylactic measures consist

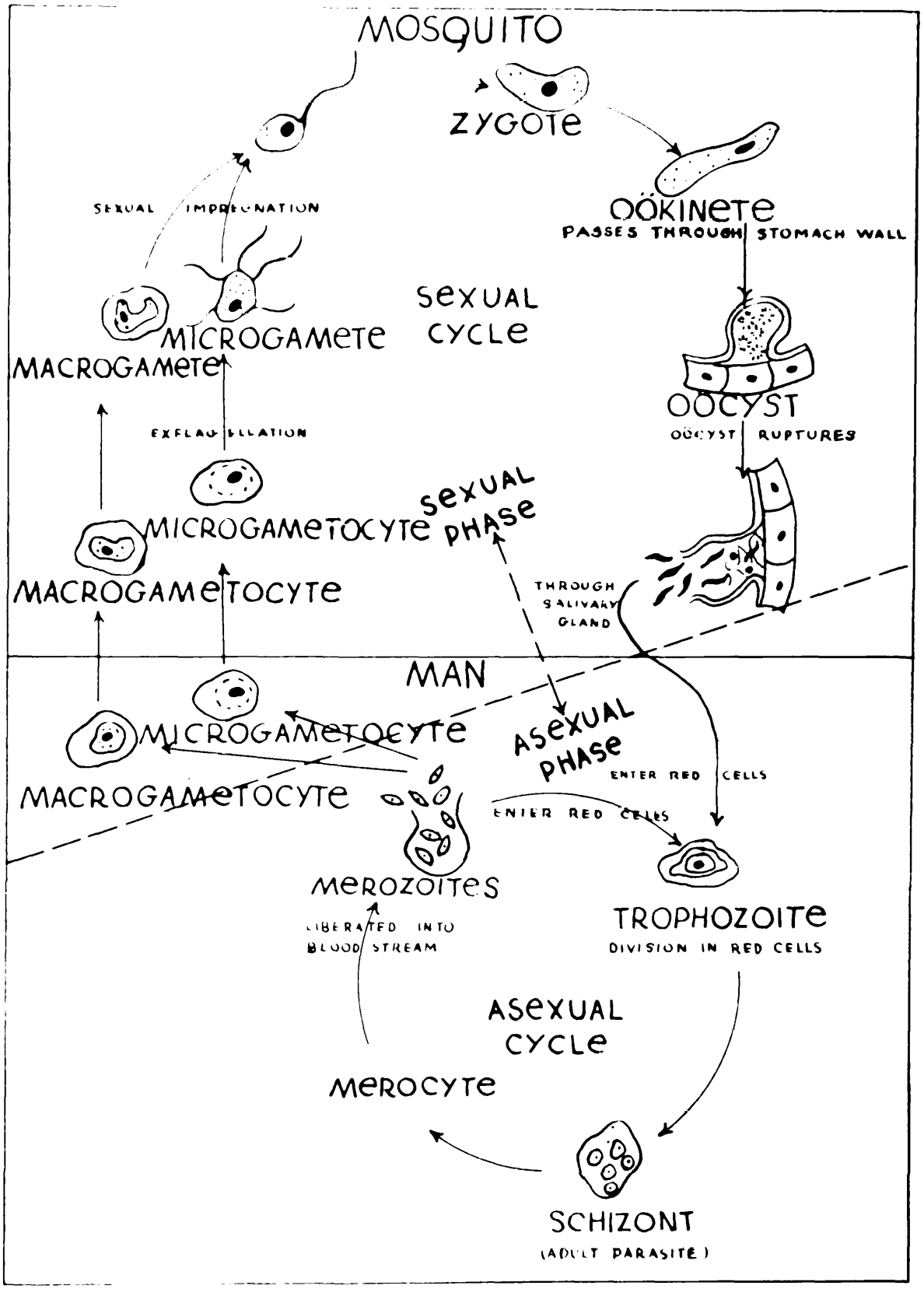


Plate 1.

Life Cycle of the Malaria Parasite

in administering drugs which would prevent infection when the subject is bitten by a malarious mosquito. Chemotherapeutic measures are aimed at destruction of sporozoites when they are injected by the mosquito (this would be real prophylaxis), elimination of the schizonts (as representative of the asexual cycle), or destruction of the gametocytes (as representative of the sexual cycle). Any drug which destroys the sporozoites prevents malaria from developing in a human or animal host. A schizonticidal drug cures the disease in the victim since it stops the asexual cycle which is responsible for the symptoms of malaria. However, even if the asexual cycle has been stopped, the gametocytes are still present and thus the host is an active source of infection to the mosquito. A gametocidal drug does not disturb the asexual cycle of the disease, and so the symptoms of malaria are not relieved. In this situation the host is no longer capable of infecting mosquitoes, and so a gametocidal drug effects prophylaxis in that it prevents the spread of the disease.

The most desirable type of drug is one which destroys the sporozoites, thus completely preventing the disease. Nearly as desirable is a drug which is both schizonticidal and gametocidal, thus relieving the symptoms of the disease and preventing its spread.

In the year 1820 Pelletier and Caventou isolated from cinchona bark the alkaloids cinchonine and quinine. This was probably the inception of chemotherapy since it was the first instance of the use in medicine of a pure chemical, toxic to the invading parasite, but relatively harmless to the host. Later, Ehrlich noted the selective staining action which certain dyes had for certain tissues (314). In 1891 Ehrlich and Guttmann showed that the malarial parasite was strongly

stained by methylene blue and thus differentiated from the tissue of the host. They then demonstrated that methylene blue exhibited some antimalarial action, but much less than that of quinine.

After much research by Skraup, Königs, von Miller, and many other workers, Rabe et al, in 1908, announced the formula for cinchonine (317), and subsequently elaborated it into a general formula for the cinchona alkaloids (316, 317, 319, 320, 321, 322, 323, 325). Although quinine has not as yet been synthesized, the total synthesis of dihydroquinine and isomerides was announced by Rabe (319) in 1931. Since 1908 many compounds of the type of quinolyl ketones and alcohols have been synthesized in order to substitute for quinine as antimalarial agents. These compounds were tested in vitro on protozoa, a procedure which is now known to be of little value, and further progress was hampered until an in vivo test was developed. Until the modern biological tests were evolved, all the early investigations on the cinchona alkaloids were performed on malaria patients. In 1907 the Sergents (361) began experimenting with bird malaria, and the work was continued by Kopaneris, Marks, Brumm, Fourneau, and others, culminated by the development by Roehl in 1924 of a standard technique for the testing of drugs as possible antimalarials by using infected canaries (329). In Roehl's test, in canaries, out of a number of birds inoculated with blood from previously infected birds, a few are left as controls and the rest receive daily, for five or six days, a dose of the drug being tested. If the drug is effective, a definite increase will be noted in the period until parasites appear in the peripheral blood. In the controls the parasites will appear in five or six days. The number of days of retardation is a measure of the efficiency of the drug. The parasites

used in the canaries are related to the species causing human malaria (e.g. Plasmodium cathemerium or Proteosoma praecox). This test does not differentiate between gametocidal and schizonticidal drugs, since in the canary all three forms, schizonts, micro- and macro-gametocytes, of the bird-malaria parasite appear in the peripheral blood. In the case of the Java sparrow (Oriscmis orisivora) infected with Haemoproteus orisiverae, a parasite similar in type to that causing malaria, only the gametocytes appear in the peripheral blood. On the assumption that a drug which is toxic to gametocytes of Haemoproteus will be toxic to those of malaria (so-far well-founded), a positive result would indicate a gametocidal drug. A schizonticidal drug will be effective in canaries but not in Java sparrows; a gametocidal drug will be effective in both. Tests for drugs in avian malaria have been developed by many workers, including Fourneau and Bovet (117) in France, Kikuth (206) in Germany (using paddy birds), Collier and Krause (80) who introduced the use of the Java sparrow in 1929, and Magidson et al in Russia who used siskins in their tests. The fact that human malarial infections are not transmittable to birds raises the serious question as to the validity of testing in birds drugs which are intended for use in human malaria. It has been shown that quinine is active both in human and in bird malaria. This was also shown to be true for alkaloids related to quinine, and for plasmochin and atabrine. However, in the case of certain sulfonamide derivatives Coggeshall of the Rockefeller Institute has found them to be inactive in bird malaria, but active in human malaria. This would indicate that perhaps certain compounds highly active in human malaria have been discarded on the basis of negative tests in bird malaria.

In view of the fact that the malaria plasmodia are very

difficult to culture, tests on related easily cultured organisms have been devised. Paramecia have been used in tests on the basis that quinine is toxic to them. Hegner, Shaw, and Manwell (146) have stated that even though this test is a poor indication of antimalarial activity they use it as a routine examination in order to get some indication of the toxicity of drugs to protozoa.

Screening tests for antimalarial drugs were extended to monkeys by Napier and Campbell and Knowles and Das Gupta (211) in 1932. Later Van Hooyen and Pile and Nicol transmitted P. knowlesi from monkeys to humans, and in 1934 Taliaferro and Cannon (301) infected malignant tertian malaria from man to apes. The use of monkeys has been particularly successful in testing sulfonamide derivatives.

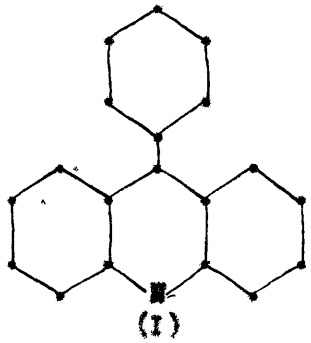
The relative measure of the efficiency of a series of drugs is given by the therapeutic index. This is the ratio of the maximum tolerated dose to the minimum curative dose. Thus, for plasmochin the therapeutic index is:

$$T.I. = \frac{M.T.D.}{M.C.D.} = \frac{0.00016}{0.000004} = 40$$

The minimum curative dose is the amount of the drug which will cause a definite retardation of the onset of disease in the case of canaries, or cause the disappearance of gametocytes in the case of the Haemoproteus infection of Java sparrows. It should be remembered that the therapeutic index is only an indication of the activity of a drug and merely affords a means of selecting compounds worthy of further testing. The indices obtained in a particular series of tests by a single investigator using a definite species of bird and a particular strain of parasite shows the relation within that series, but it is not possible to easily compare tests on different birds and by different investigators since the index

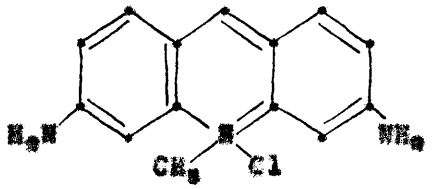
on the same drug will be found to vary among a group of experimenters. Thus, Fourneau obtained a therapeutic index of 40 for plasmochin when tested on Java sparrows, whereas Roehl (329) obtained an index of 30 for plasmochin when tested on canaries. Another rough quantitative measure of these drugs is the quinine equivalent, an expression which is used for the comparison of the various cinchona alkaloids. Quinidine has a quinine equivalent of about 0.5, cinchonidine about 0.5, dihydroquinine 1 to 2, etc.

The use of pure quinine in 1820 by Pelletier and Caventou was the first instance of the use of a pure chemical in chemotherapy. This was followed in 1880 by the preparation of 2,4-dioxy-3,4-dihydro-6-methoxyquinoline by Einhorn (99P), which chemical was later shown to possess antimalarial activity. In 1891 Guttmann and Ehrlich (140) demonstrated that methylene blue could be used in the treatment of malaria, but that it was not as active as quinine. In 1897 Monocorvo (281) found that 5-benzoylamino-8-ethoxyquinoline (Analgen) was useful in treating malaria, and Mannaberg (249) made similar claims for 2-methyl-4-phenylquinoline. In this same year Mannaberg (249) introduced the first compounds of the acridine series for use in malaria therapy. He studied the action on the malarial parasite, as well as other types of infective agents, of derivatives of the "phosphine" nucleus (I).



(I)

The most important problem in the following years was the elucidation of the structure of the cinchona alkaloids, and in 1906 their constitution was announced by Rabe, Skraup, Königs, von Miller, etc. From then until the first World War research was directed toward modification of the basic structure of the cinchona alkaloids. The first published work on these synthetically-altered alkaloids was that of Kaufmann (197) in 1919. The great incentive for the synthesis of a substitute for quinine, as related by Yorke (401), came as a result of Germany's inability to obtain cinchona alkaloids during the first World War. The work until this time had been of a varied and haphazard nature as shown by the report in 1918 by Häussler (144) that a bone distillate containing many quinoline compounds, called "Dippel's Oil", was the best substance available for the treatment of intermittent fever; and that by Kalberlah and Schlossberger (194) in which it is stated that trypaflavin (II) is inactive in malaria.

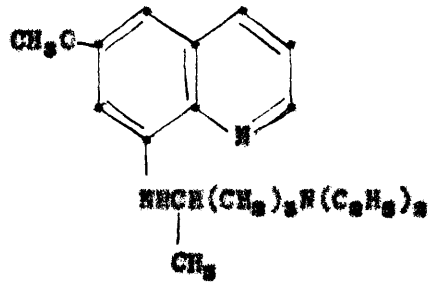


(II)

Eisleb (100) has stated that, until the development by Roehl (329) in 1926 of a method for evaluating antimalarial activity of drugs in birds, the lack of a proper test hindered investigation of antimalarial properties of the compounds which had been synthesized. Until this time the main work in the acridine series, for example, had been devoted to the production of antiseptic properties in the compounds. The concentrated efforts of the workers in the I. G. Farbenindustrie finally resulted in the preparation of Plasmochin* (Plasmoquine) (III) in 1926, the chemical

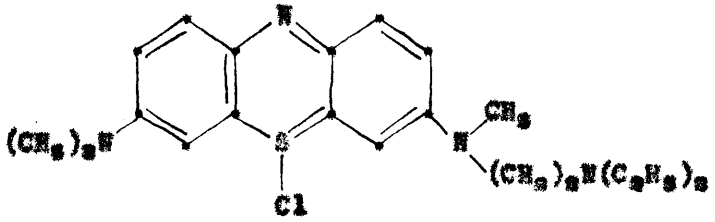
*Plasmochin has been given the non-proprietary name of pamaquine. The name Plasmochin is registered in the U. S. Patent Office.

and antimalarial properties of which were published by Merlein (152, 154), Roehl (329, 330), Sioli (368, 369) and Mühlens (287, 288).



(III)

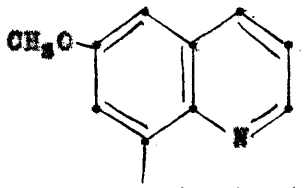
However, the structure of Plasmochin was not revealed until 1926, by Merlein (153). In publications by Schulemann, Schönhöfer and Wingler (344, 345, 354, 355) the reasoning which was followed in the production of Plasmochin was given as follows: From the work of Guttmann and Ehrlich (140) it was known that methylene blue had a specific action on the plasmodia of malaria and had indeed been used along with quinine in the treatment of malaria (406). They then replaced one of the $-NMe_2$ groups in methylene blue with various dialkylaminoalkylamino groups to produce a compound, such as (IV), with enhanced activity (359F).



(IV)

Next they tried the introduction of similar chains into various heterocyclic nuclei, especially those which showed some antimalarial action of their own. It had been found earlier by Schulemann, Schönhöfer and Mietzsch (350F), that 6-methoxy-8-aminoquinoline exerted "a strong specific destroying action on blood parasites," and so they prepared a large number of 6-alkoxy-8-dialkylaminoalkylaminoquinolines. The compound they began with, 6-methoxy-8-(β-diethylaminoethylamino)-

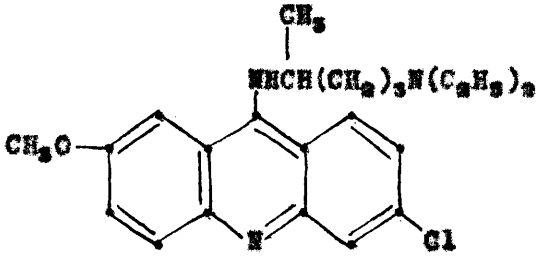
quinoline (V), was found by Roehl to be very active in bird malaria in canaries.



$NH(CH_2)_2N(C_2H_5)_2$ (V)

Schulemann (344, 345) stated that 12,000 compounds were synthesized before the optimum relation between activity and toxicity was found, in the compound which they named Plasmochin. Almost none of this work which had been carried out in the I. G. Farbenindustrie is to be found described in the journals, and what little has been revealed may be found in the patent literature (58P, 353P, 356P, 358P).

On the basis of the striking success obtained by attaching the dialkylaminoalkylamino side-chain to 6-methoxyquinoline, it was a logical development to introduce similar chains into other heterocyclic nuclei. This work led to the synthesis of Atebrin (Atabrine*) (VI) by Mauss and Rietzsch (263P), reported in 1932. The biological work was carried out by Kikuth (206), successor to Roehl, who found it to be less toxic than Plasmochin, but instead of being gametocidal like Plasmochin it is schizonticidal and thus resembles quinine in action. The actual revelation of the structure of Atabrine was not made until 1933 (265, 272).



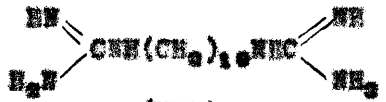
(VI)

---

*Atabrine has been given the non-proprietary name of quinacrine hydrochloride. The name Atabrine is registered in the U. S. Patent Office.

The direction of investigations since the synthesis of Plasmochin and Atabrine has largely been the variation of the sidechain, the position of the sidechain, the type of alkoxy group, and the position of the alkoxy group. Much of this work has been done by groups of experimenters led by Fourneau in France, Robinson in England, and Magidson in Russia.

A class of compounds of recent development which exhibit antimalarial properties are the amidines. The earliest report of the use of amidine compounds in malaria therapy was that of Easson and Fyman in 1931 (96) who obtained negative results in bird malaria in the tests on three amidines. The situation remained like this until 1937 when King, Lourie and Yorke re-examined the use of amidines, guanidines, iso-thioureas, and similar compounds (208) on trypanosomal infections in mice. The connection between trypanosomal and malarial infections, as related by Yorke (401), is the hypoglucosis which results from both. The existence of trypanosomes depends on the presence of glucose, and it was known that feeding of glucose to canaries infected with malaria resulted in an increase in the number of parasites and usually death to the host. It was shown that synthalin (VII) has a direct action on T. equinum, and so in 1938 Glyn-Hughes, Lourie and Yorke tested 1,11-diamidinoundecane,



(VII)

the most potent of a group of normal alkylene diamidines tested against trypanosomiases, on malaria infections in canaries and found it to be inactive. However, when this compound was tried on P. knowlesi in monkeys or P. vivax in man it was found definitely active.

Of very recent innovation is the investigation of the various sulfonamides as antimalarial agents. Mietzsch and Mauss (276P, 277P)

were the first to prepare compounds of this type for combating blood parasites, but the first reported tests of sulfonamides against malaria were by de Leon (227) and van der Wielen (387). A voluminous account of discussion has been published since then debating the value of sulfonamides for the treatment of malaria, and although it has been definitely shown that some of these compounds are active, the matter requires more investigation. One of the difficulties encountered has been the failure of some of these drugs in avian malaria, but success in human malaria. Sulfadiazine (VIII) has been shown by Coggeshall, Maier and Best (77) to be effective against malaria in man.

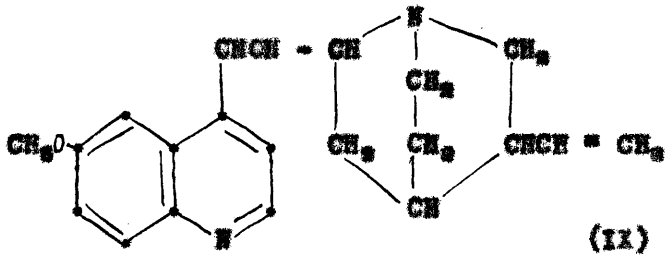
(VIII)

Literature Review

An extensive review has been made of the literature relating to compounds which have been prepared for use as antimalarials and those which have been tested for antimalarial activity. These compounds may be classified under the following headings: natural alkaloids and related synthetic compounds, quinoline derivatives, acridine derivatives, and miscellaneous compounds. Syntheses of some of the antimalarials will be discussed and only representative examples of the various types of compounds will be tabulated. Many excellent detailed reviews are available and the references given in this paper will be sufficient to afford an introduction to nearly all the published work on this subject. A more detailed listing of compounds is considered to be unnecessary repetition.

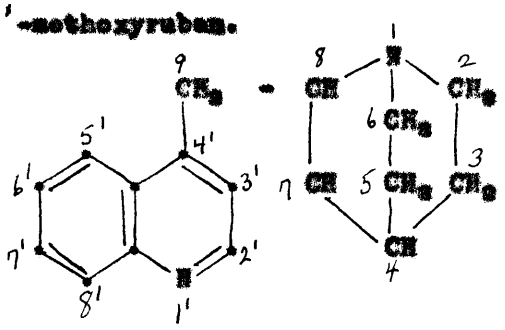
Natural Alkaloids and Related Synthetic Compounds

Although it has been reported that certain isolated alkaloids possess antimalarial activity, it is indisputably known that the cinchona alkaloids possess very high curative value for malaria. The most important of the cinchona alkaloids is quinine (IX).



(IX)

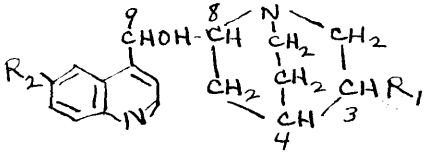
The cinchona alkaloids may be considered as derivatives of the parent substance ruban (924) (X). Thus, quinine would be 3-vinyl-9-hydroxy-6'-methoxyruban.



(X)

Table 1

Cinchona Alkaloids
(Naturally Occurring)



Name	R_1	R_2	Direction of Rotation C_3 C_4 C_8 C_9	$[\alpha]_D$	Quinine Equivalent	Reference
Cinchonine	$-CH{=}CH_2$		+ − + +	+224.4	< 0.2	55
Cinchonidine	$-CH{=}CH_2$		+ − − −	-111	0.5	55
Cupreine	$-CH{=}CH_2$	-OH	+ − − −	-284.5	0.98	132
Quinine	$-CH{=}CH_2$	$-OCH_3$	+ − − −	-158.2	1	55. 79. 115. 132
epiquinine	$-CH{=}CH_2$	$-OCH_3$	+ − − +	+ 43.9	0.1	54
Quinidine	$-CH{=}CH_2$	$-OCH_3$	+ − + +	+243.5	0.5	55. 132
epiquinidine	$-CH{=}CH_2$	$-OCH_3$	+ − + −	+102.4	0.1	54
Dihydrocinchonine	$-CH_2CH_3$		+ − + +	+200	< 0.2	55. 132
Dihydrocinchonidine	$-CH_2CH_3$		+ − − −	- 95	< 0.2	55. 132
Dihydroquinine	$-CH_2CH_3$	$-OCH_3$	+ − − −	-142.5	1.35	54. 132. 319
epiDihydroquinine	$-CH_2CH_3$	$-OCH_3$	+ − − +	+ 32.5	1.0	54
Dihydroquinidine	$-CH_2CH_3$	$-OCH_3$	+ − + +	+237.5	0.81	54. 132. 319

Table 1 (cont'd.)

Cinchona Alkaloids
(Naturally Occurring)

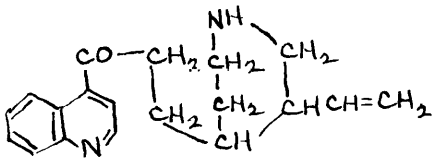
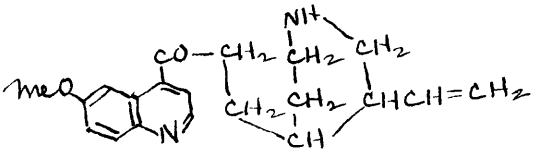
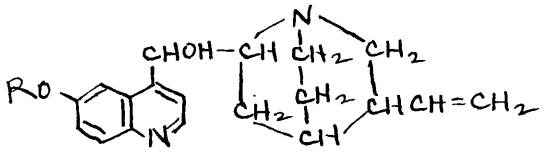
Name	Structure	Quinine equivalent	Reference
Cinchonicine (Cinchotoxine)		0 slight	192
Quinicine (Quinotoxine)		0	54, 192

Table 2

Synthetic Derivatives of Cinchona Alkaloids

a. Alkyl Cupreines

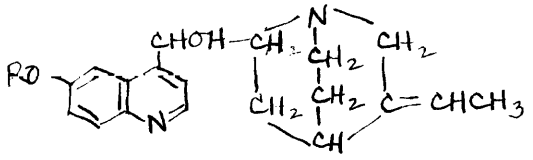


Name	R	Activity	Reference
Cupreine	H-	±	192
Quinine	CH_3-	+++	192
Quinidine	CH_3-	+++	192
Quinethylene	C_2H_5-	+++	190, 192
Quinpropylene	C_3H_7-	+	192
Quinallylene	CH_2=$CHCH_2$-	+	192
Quinamylene	C_5H_{11}-	+	192

Table 3

Synthetic Derivatives of Cinchona Alkaloids

b. Alkyl Apoquinines

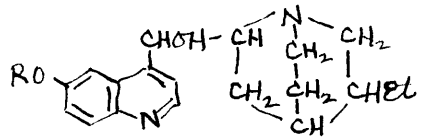


Name	R	Quinine Equivalent	Reference
Apoquinine	H-	0.98	54
Methylapoquinine	CH_3-	0.69	54
Ethylapoquinine	C_2H_5-	1.18	54
Butylapoquinine	C_4H_9-	1.1	54
Hexylapoquinine	C_6H_{13}-	1.72	54
Undecylapoquinine	$C_{11}H_{23}$-	0.75	54
Apoquinidine	H-	0.4	54
Methylapoquinidine	CH_3-	1.0	54

Table 4

Synthetic Derivatives of Cinchona Alkaloids

c. Alkyl Hydrocupreines

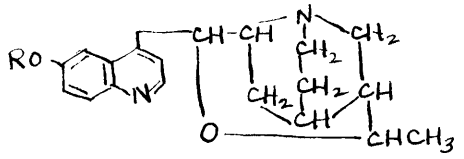


Name	R	Quinine Equivalent	Reference
Dihydrocupreine	H-	0.92	54
Ethyldihydrocupreine (Optochin)	C_2H_5-	1.05	54. 374
Amyldihydrocupreine	C_5H_{11}-	1.93	54
Isoamyldihydrocupreine (Eucupin)	iso-C_5H_{11}-	1.89	3. 54
Cetyldihydrocupreine	$C_{16}H_{33}$-	1.43	54
Isocetyldihydrocupreine (Vusin)	iso-$C_{16}H_{33}$-	1.9	191

Table 5

Synthetic Derivatives of Cinchona Alkaloids

d. Alkyl isoapoQuinidines

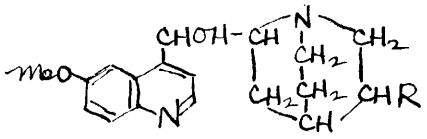


Name	R	Quinine Equivalent	Reference
isoapoquinidine	H-	0.11	54
Methyl isoapoquinidine	CH_3-	0.1	54
Ethyl isoapoquinidine	C_2H_5-	0.25	54
Cetyl isoapoquinidine	$C_{16}H_{33}$-	0	54

Table 6

Synthetic Derivatives of Cinchona Alkaloids

e. Changes of the Vinyl Group

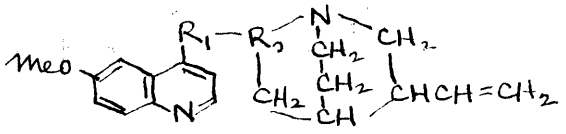


Name	R	Quinine Equivalent	Reference
Dehydroquinine	-CHCH		132
Dihydroquinine	$-CH_2CH_3$	1.35	54, 132, 319
β-Chlorodihydroquinine	$-CH_2CH_2Cl$	1	132
α-Chlorodihydroquinine	$-CHClCH_3$	sl. 1	130
α,β-Dibromodihydroquinine	$-CHBrCH_2Br$	sl. 1	130
α-Hydroxydihydroquinine	$-CHOHCH_3$	0.54	54
Quitenamide	$-CONH_2$	0	79
Quitenmethylamide	$-CONHCH_3$	0	79
Quitenine	-COOH	0	79, 196
Quitenineethylester	$-COOC_2H_5$	0.5	196
Quitenineisoamylester	-COO-iso-C_5H_{11}	0.5	55, 196
Quitenidine	-COOH	0	196
Quitenidineethylester	-COOEt	0	196

Table 7

Synthetic Derivatives of Cinchona Alkaloids

f. Changes of the -CHCH- bridge

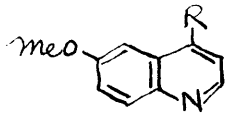


Name	R_1---R_2	Activity	Reference
Quinine chloride	-CHCl-CH	0	79
Quinene	-CH=C	0	79
Desoxyquinine	$-CH_2-CH$	0	112
Quininone	-CO-CH	0	112
Quinine amine	$-CHNH_2-CH$	0	120

Table 8

Synthetic Derivatives of Cinchona Alkaloids

g. Miscellaneous Compounds



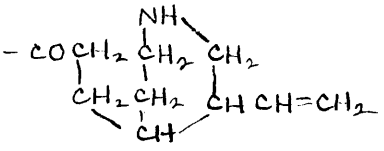
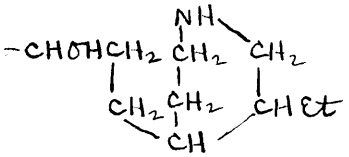
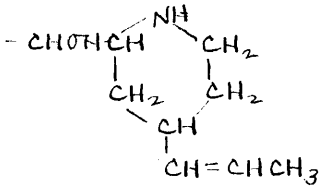
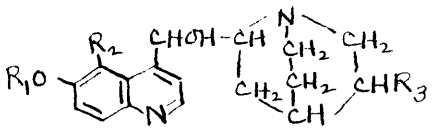
Name	R	Quinine Equivalent	Reference
Quinotoxine (Quinicine)		0	139
d-Dihydroquinicinol		0	41

Table 8 (cont'd)

Name	R	Quinine Equivalent	References
Pseudoquinidine		0.79	54
Niquine		0.08	54, 127
Niquidine		1.45	54, 127



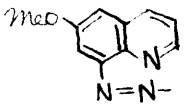
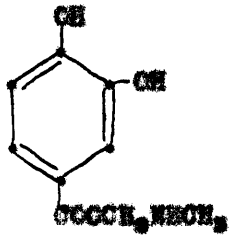
Name	R_1	R_2	R_3	Quinine Equivalent	References
5'-Bromodihydroquinine	CH_3-	-Br	$-CH_2CH_3$	0	115
5'-Nitrodihydroquinine	CH_3-	$-NO_2$	$-CH_2CH_3$	0	192
5'-Phenylazocupreine	H-	$-N{=}NC_6H_5$	$-CH{=}CH_2$	<1	129
5'-(6-Methoxy-8-quinolyl)-azohydrocupreine	H-		$-CH_2CH_3$	<1	191P

Table 2

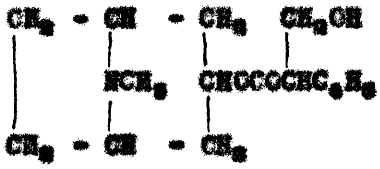
Miscellaneous Alkaloids

Name	Activity	Reference
Adrenalin	no direct action	360
Aspidosperminine	active	88
Atropine	--	364
Berberine	none	136
Cedrin	active	293
Cocaine		364
Codeine		364
Eohitamine	slight	136
Harmineol	none	81
O-Diethylaminoethyl harmineol	none	81
Harmaline	none	81
Hyoscyamine	active	337P
Morphine		28
Papaverine	none	136
Pilocarpine		379P
Pyrethine	none	115
Sinine	active none	229,230 136
Sparteine	none	136
Strychnine		364
Vitex	active	333
Yohimbine		379P

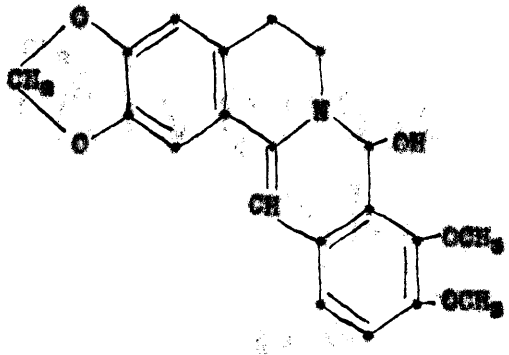
Adrenalin:



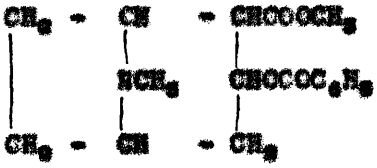
Atropine: d,l-tropyltropine



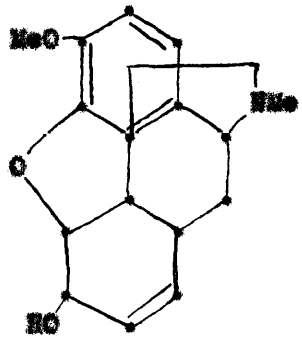
Berberine:



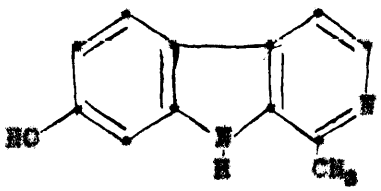
Cocaine:



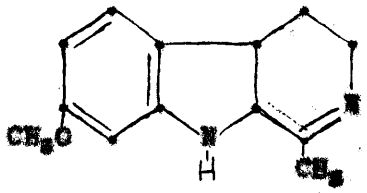
Codeine:



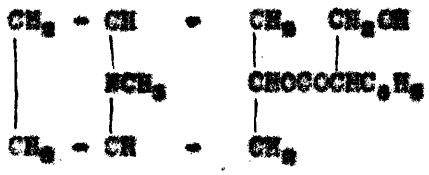
Harmineol:



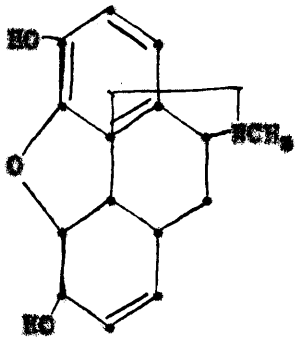
Harmaline:



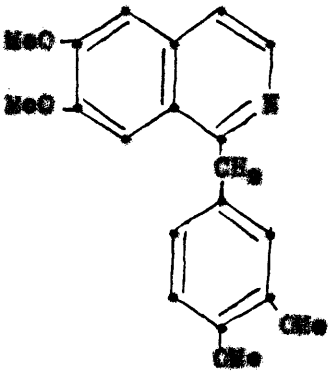
Hyoscyamine: laevo tropyltropine



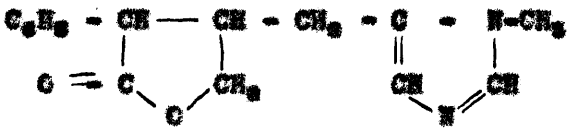
Morphine:



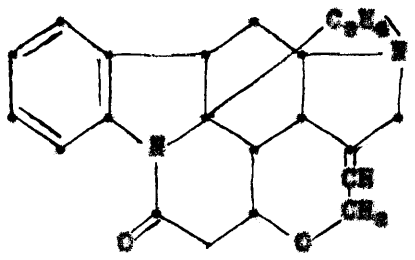
Papaverine:



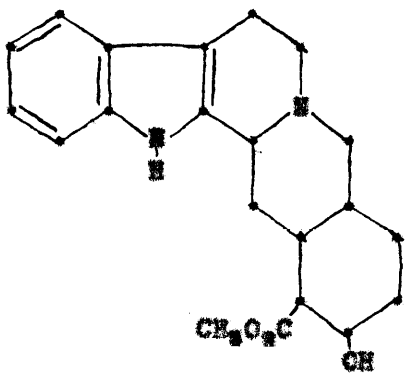
Pilocarpine:



Strychnine:



Yohimbine:



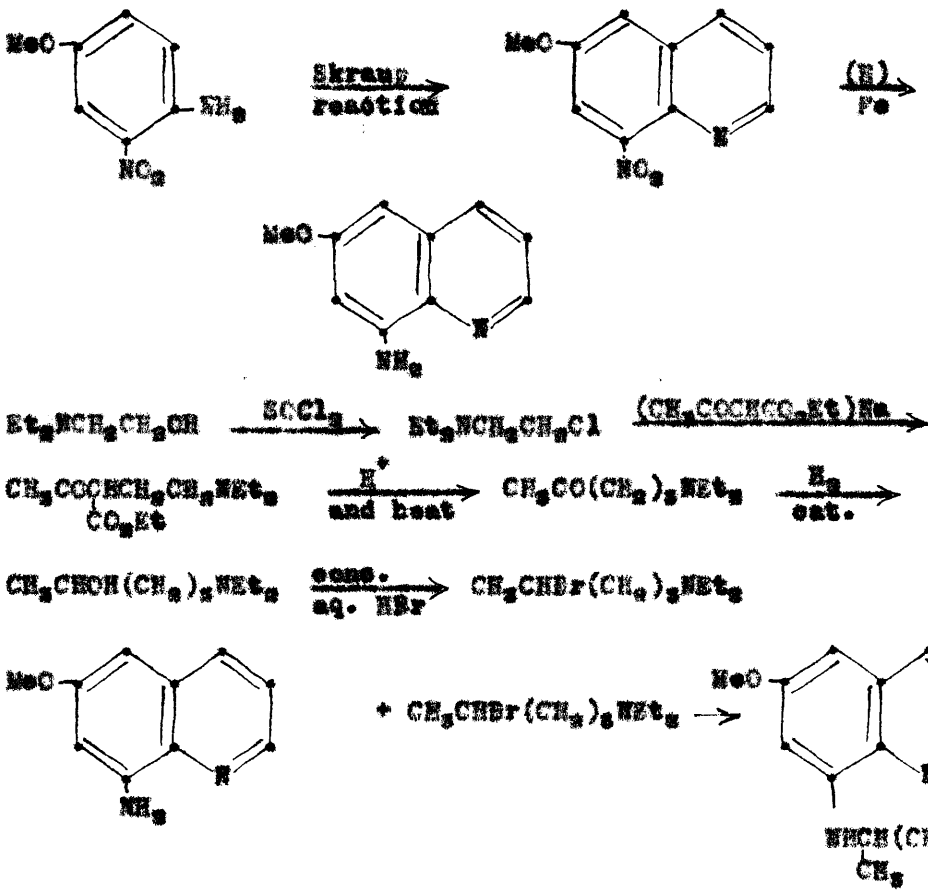
From the above tables it is evident that the only important alkaloids possessing antimalarial action are the cinchonas and their derivatives. The important variations of these compounds are those involving the vinyl group, the secondary alcohol group, the phenolic ether group, substitution in the 5′ position, and stereoisomeric relations. The vinyl group appears to be of minor importance; hydrogenation increases the activity (quinine, hydroquinine; cupreine, hydrocupreine), but when the vinyl compound possesses no activity hydrogenation does not produce activity (cinchonine, hydrocinchonine). Antimalarial activity still persists when water, hydrogen halide, halogen, and ammonia are added to the double bond (quinine, hydrochloroquinine, hydrobromoquinine, amino quinine, hydroxyquinine), but oxidation to a carboxylic acid eliminates activity while esterification of the acid partially restores it (quinine, quitenine, ethylquitenine). Any change in the secondary alcohol group completely destroys antimalarial activity, this even holding true for acetylation (quinine chloride, desoxyquinine, quinone, acetylquinine). The methoxy group in quinine is not essential for activity, but enhances it; introduction of the ethoxy group in place of the methoxy group affords an increase in action, but further increase in size of the alkoxy group decreases the activity (cupreine, quinine, cinchonine, ethoxycinchonine, methoxycinchonine, propyloxycinchonine, allyloxycinchonine). Substitution

in the 5' position with an amino group, halogen, or an azo group does not substantially decrease the activity (5'-aminohydroquinine, 5'-phenylazo-cupreine). No definite conclusions may be based on optical activity of the cinchona alkaloids and their derivatives. l-Quinine and l-dihydroquinine are about twice as active as d-quinidine and d-dihydroquinidine respectively, and similarly l-cinchonidine is more than twice as active as d-cinchonine, but the d-quinine-isomer, methyl-apoquinidine, is more active than either of its l-isomers, α- or β-isoquinine. More surprising is the fact that epiquinine and epiquinidine, the C_8 epimerides of quinine and quinidine respectively, are only one-tenth and one-fifth as active as their epimers.

Quinoline Derivatives

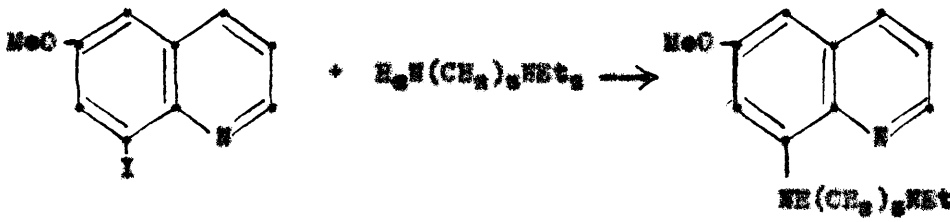
The derivatives of quinoline compose the largest single group of compounds which have been studied for antimalarial properties. Of these compounds most are derivatives of 8-aminoquinoline, similar to Plasmochin. Investigations on quinoline compounds have been mainly concerned with the effects of variation of the alkylamine side-chain, by varying the length, degree of branching, and type of terminal dialkylamino group, and by altering the 6-alkoxy group.

Plasmochin, the most popular antimalarial of this group, was first synthesized in the laboratories of the I. G. Farbenindustrie in 1924, and is now being produced commercially in the United States by the Winthrop Chemical Company. The synthesis (963) involves the following steps:



The nitroanisidine is available out of the dyestuff industry and the diethylaminoethanol has been commercially available for years as an intermediate for the local anesthetic procaine.

Many of the variations of the Plasmochin model are those in which the dialkylaminoalkylamine side-chain is modified. The final product is made by reacting the 8-aminoquinoline with the dialkylaminoalkyl halide. Owing to polymerization of the aminoalkyl halide the yield is not very high. This difficulty could conceivably be overcome by reacting an 8-bromoquinoline with the dialkylaminoalkylamine, but the bromine in the 8-position in quinoline is too unreactive. However, Knunyants (212) has reacted 8-iodo-6-methoxyquinoline with 5-diethylaminoamylamine:



Various dialkylaminoalkyl halides have been prepared by the following methods: The syntheses generally involve first the preparation of a glycol by reduction of the ester of a dibasic acid (6, 296):

$$EtO_2C(CH_2)_{8,10,14}CO_2Et \xrightarrow[EtOH]{Na} HO(CH_2)_{7,8,9}CH$$

The glycol is either converted to the halogenohydrin or the dihalide. The halogenohydrin is acetylated, reacted with a secondary amine, hydrolyzed to the amino alcohol, and then converted to the aminoalkyl halide.

(305):

$$HO(CH_2)_3CH + HCl \longrightarrow Cl(CH_2)_3CH + H_2O$$

Doriek and Bissell (85):

$$Cl(CH_2)_3CH + CH_3CO_2H \xrightarrow{H^+} Cl(CH_2)_3OCOCH_3 + H_2O$$

Enunyants and Benevolenskaya (215):

$$Cl(CH_2)_3OCOCH_3 + Et_2NH \longrightarrow Et_2N(CH_2)_3OCOCH_3 \xrightarrow[NaOH]{H_2O}$$

$$Et_2N(CH_2)_3OH \xrightarrow{SOCl_2} Et_2N(CH_2)_3Cl.HCl$$

Slotta and Behmisch (274):

$$Et_2N(CH_2)_3OH \xrightarrow{SOCl_2} Et_2N(CH_2)_3Cl.HCl$$

Magidson and Strukov (249):

$$Et_2N(CH_2)_3OH \xrightarrow{SOCl_2} Et_2N(CH_2)_3Cl.HCl$$

Farbwerke vorm. Meister Lucius and Brüning (107F):

$$Et_2N(CH_2)_3OH.HBr \xrightarrow[48\% HBr]{boil} Et_2N(CH_2)_3Br.HBr$$

If the dihalide is used the course of reactions is to convert it to a phenoxyalkyl halide, which is reacted with a secondary amine to produce the dialkylaminoalkyl phenyl ether. Boiling this product with a halogen acid produces the desired halide. The phenoxyalkyl halide is more advantageously prepared from the halogenohydrin by reacting with sodium phenoxide and then with thionyl chloride, thus avoiding the loss in yield experienced by obtaining a diphenoxyalkane as a byproduct when the dihalide is used. The dialkylaminoalkyl halide may be obtained by direct reaction of trimethylene chlorobromide with a secondary amine, but the possibility exists of forming the disubstitution product.

(298):

$$HO(CH_2)_3OH \xrightarrow[H_2SO_4]{HBr} Br(CH_2)_3Br$$

(309):

$$Br(CH_2)_3Br + C_6H_5ONa \longrightarrow Br(CH_2)_3OC_6H_5 + C_6H_5O(CH_2)_3OC_6H_5$$

Marvel, Zartman and Blatchardt (258):

$$Br(CH_2)_3OC_6H_5 + Et_2NH \longrightarrow Et_2N(CH_2)_3OC_6H_5 \xrightarrow{HBr} Et_2N(CH_2)_3Br.HBr$$

Slotta and Behmisch (274):

$$Br(CH_2)_3OC_6H_5 + Et_2NH \xrightarrow{140^\circ} Et_2N(CH_2)_3OC_6H_5 \xrightarrow[conc.\ HCl]{160^\circ}$$

$$Et_2N(CH_2)_3Cl$$

Magidson, Strukov, Robuishev and Torf (244):

$$Br(CH_2)_3Cl + Et_2NH \longrightarrow Et_2N(CH_2)_3Cl$$

Dialkylaminoalcohols have been prepared in good yield by reacting a secondary amine with ethylene oxide or epichlorohydrin.

Headlee, Collett and Lazzell (145):

$$Et_2NH + CH_2\!-\!CH_2 \longrightarrow Et_2N(CH_2)_2OH$$

Blicke, Parke and Jenner (39):

$$Bu_2NH + CH_2\!-\!CHCH_2 \longrightarrow Bu_2NCH_2CHOHCH_2$$

Ruberg and Shriner (394):

$$Et_2N(CH_2)_2OH + CH_2\!-\!CH_2 \longrightarrow Et_2N(CH_2)_2O(CH_2)_2OH$$

Mieleb (101F):

The malonic ester condensation has been used to add two carbons to the aminoalkyl halide.

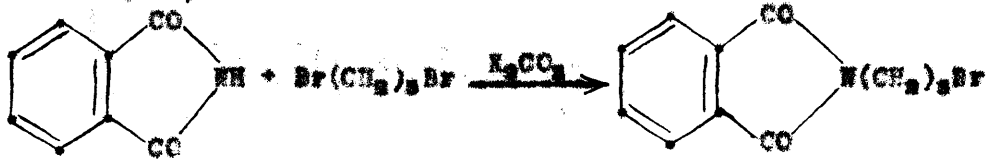
Magidson and Strukov (243):

$$Et_2N(CH_2)_3Cl + Na[CH(CO_2Et)_2] \longrightarrow Et_2N(CH_2)_3CH(CO_2Et)_2 \rightarrow Et_2N(CH_2)_4CO_2H$$

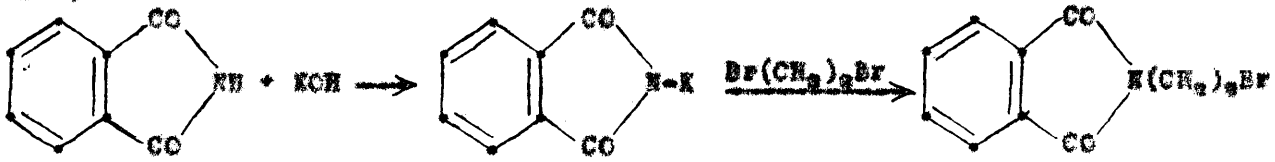
$$\longrightarrow Et_2N(CH_2)_4CO_2Et \xrightarrow{(H)} Et_2N(CH_2)_5OH$$

In preparing some of the simpler aminoalkylaminoquinolines use has been made of the phthalimide synthesis.

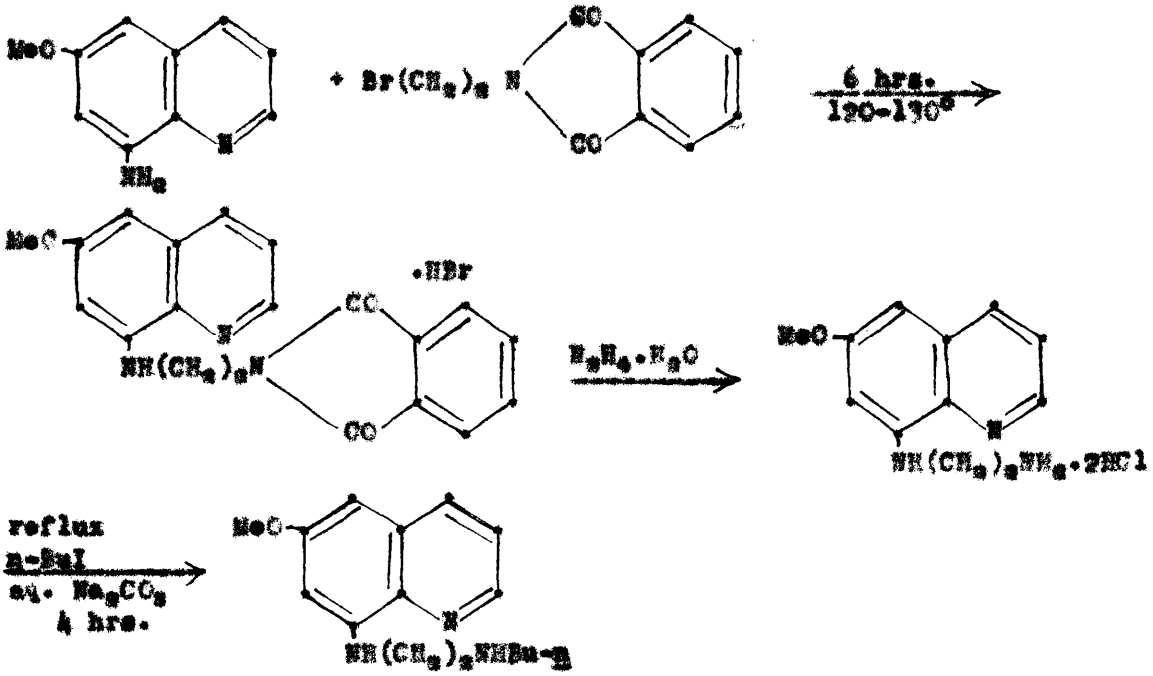
Ing and Manske (181):



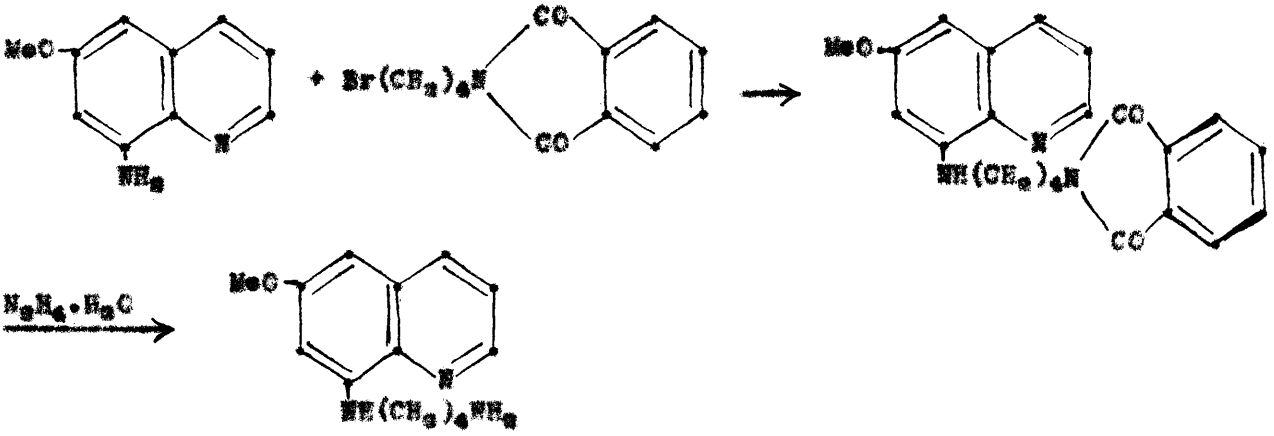
(900):



Seshadri (962):



Baldwin and Robinson (14):

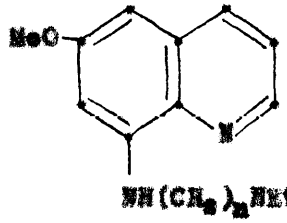


In illustrating the effect of the length of the alkylamine side-chain on the therapeutic index a series of 6-methoxy-8-diethylaminoalkylaminoquinolines have been chosen. The tests were made on Java sparrows by Altman and by Fourneau, on siskins on Magidson's compounds by Krichevskii, and on canaries by Bovet. In tests on Java sparrows a maximum of 180 is reached where n = 9 (Table 10). This same compound gives a maximum therapeutic index when tested in siskins, but the index is only 40.

Since the compounds where n = 7, 8, and 9 were tested on Java sparrows by Altman, and the others of the series were tested on Java sparrows by Fourneau, a strict comparison in the series is prevented, but it may be assumed that the maximum is afforded in the 9 compound. It is of interest to note that the indices for the compounds where n is odd are higher than adjacent compounds where n is even. This holds true for tests on both Java sparrows and on siskins. It is of further interest to note that the indices obtained where the Java sparrow was the test bird are all much higher than those obtained on siskins. This clearly shows that these compounds have higher gametocidal activity than schizonticidal.

Table 10

Effect of the Length of the Alkylamino Side-Chain in the 6-Methoxy-8-Aminoquinolines

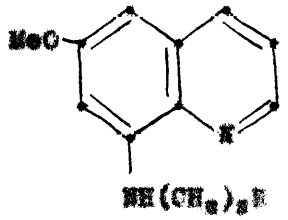


n	Therapeutic Index: Java Sparrows	Therapeutic Index: Sinking	Therapeutic Index: Canaries	References
2	40	6		117,118
3	100	26.5		117,118,249,271
4	10, 11, 20	10.6		39,118,210,249
5	150	25		117,118,249
6	150	13.9		39,118,222,240
7	166	33.3	1000	6,39,222,240
8	175		500	6
9	180	40	700	6,39,240
11	9-10	5.0	100	39,40,240

The effect of the terminal basic group of the alkylamino-alkylamino side-chain cannot be evaluated due to the insufficient number of compounds available for comparison. In addition to the groups listed in Table 11, various compounds have been made which have other basic groups such as piperidyl, piperazyl, lupinyl, morpholinyl, and higher dialkylamino groups.

Table 11

Effect of the Terminal Basic Group

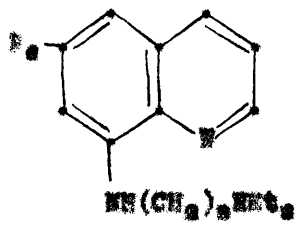


R	Therapeutic Index			References
	Siskins	Canaries	Java Sparrows	
$-NH_2$	19.3	16		13,183,734,382
$-NHC_2H_7-n$		8		382
$-NHC_4H_9-n$		8		382
$-N(CH_3)_2$	16.5		10	118
$-N(C_2H_5)_2$	26.6		100	117,118,721,243

The potency of quinoline derivatives in which there are variations in the 6-alkoxy group has been studied. It is evident (Table 12) that the methoxy group, present in plasmochin and quinine and atebrin, is not necessary for activity because the compounds in which there is an hydroxy or ethoxy group are still active. However, the methoxy derivatives are generally the most active. In the case of the higher ethers the activity completely disappears.

Table 12

Effect of Change in the 6-Alkoxy Group

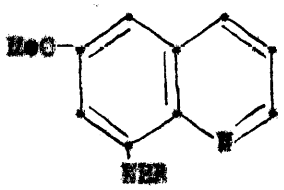


R_6	Therapeutic Index		References
	Java Sparrows	Siskins	
-H	±	0	221,242
-OH		13.3	117,221
$-OCH_3$	40	6	117,118
$-OC_2H_5$	4	4	117,221,305
$-OC_3H_7$-n		1	221,242
$-OC_3H_7$-iso		0	221,242
$-OC_4H_9$-n		1	221,242
$-OC_5H_{11}$-iso		0	221,242
$-OC_6H_{13}$-iso		0	221,242
-O-allyl		0	221,242

In order to show the effect of branching in the side-chain, Table 13 lists a series of 6-methoxy-8-diethylaminoalkylaminoquinolines. Tests on Java sparrows indicate that any branching of the side-chain has a diatherapeutic effect. This is also shown in tests on siskins, except in the case of the introduction of an alpha-methyl group where there is a rise in the therapeutic index.

Table 13

Effect of Branching in the Alkylamine Side-Chain in the 6-Methoxy-8-Diethylaminoalkylaminoquinolines



R	Therapeutic Index		References
	Sinkins	Java Sparrows	
Amyl side-chain:			
$-CH_2CH_2CH_2CH_2CH_2NEt_2$	25	150	118,243
$-CH(CH_3)CH_2CH_2CH_2NEt_2$ (Plasmochin)	40	40	117,221
$-CH(C_2H_5)CH_2CH_2NEt_2$	--	4	117,118
$-CH\left[CH(CH_3)_2\right]CH_2NEt_2$	0	--	221,235
$-CH_2C(CH_3)_2CH_2NEt_2$	2	40	117,118
Butyl side-chain:			
$-CH_2CH_2CH_2CH_2NEt_2$	10.6	20	39,118,210,243
$-CH(CH_3)CH_2CH_2CH_2NEt_2$ (Certuna)	25	10	117,222
$-CH_2C(CH_3)_2NEt_2$	2		221
Propyl side-chain:			
$-CH_2CH_2CH_2NEt_2$ (Plasmocide)	26.6	100	117,118,221,243
$-CH(CH_3)CH_2NEt_2$		10	118,222,234

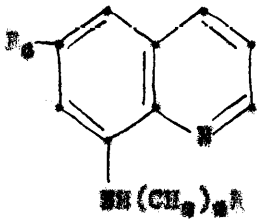
In the following series of tables, 14 through 21, are listed some of the 8-substituted quinoline derivatives, classified as to type of side-chain. In many cases there is insufficient data on the therapeutic indices from which to draw any conclusions. In the group of 8-aminoethylaminoquinoline compounds (Table 14) it may be judged that the 6-methoxy and 6-hydroxy-8-(β-diethylaminoethylamino)-quinolines are the most potent antimalarials. Among the 8-aminopropylaminoquinoline compounds (Table 15) the most active are the 6-hydroxy and 6-methoxy-8-(γ-dimethylamino-, and γ-diethylaminopropylamino)-quinolines. The indices for some of the homologs with 7, 8, 9, and 11 carbon atoms are listed (Table 18) as 100 to 1000, whereas plasmochin is only about 30. Even though these values are not directly comparable there would seem to be great promise for the higher derivatives.

The side-chain in position 8 may be interrupted with a N, S or O atom and still retain its activity (Table 19). A hydrogen of the side-chain may be substituted with an hydroxy group without destroying activity; however, etherification of the hydroxy group reduces the potency.

Unless the side-chain is attached to the ring through a secondary nitrogen atom an inactive compound results. No other substituent has been found which imparts any outstanding activity to the 8-substituted quinoline nucleus.

Table 14

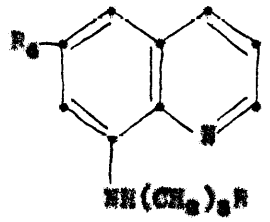
8-Aminoethylaminoquinoline Compounds



R	R_6	Therapeutic Index: Canary	Therapeutic Index: Java Sparrow	Therapeutic Index: Sickin	References
NH_2		+			19,24,352P
NH_2	OMe	2			19,352P,382
NH_2	OEt	+			19
NH_2	O-n-C_4H_9	8			382
NH-n-C_4H_9	OMe	2			382
NH-n-C_4H_9	O-n-C_4H_9	4			382
NEt_2	OH			13.3	221,242
NEt_2	OMe	8	40	6	117,118,229,235
NEt_2	OEt			4	117,221,242,243
NEt_2	O-n-C_3H_7			1	221,242
NEt_2	O-n-C_4H_9			1	221,242
N(iso-C_5H_{11})$_2$	OMe		4		115

Table 15

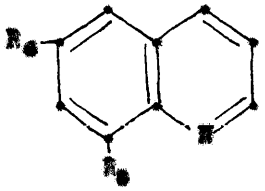
8-Aminopropylaminoquinoline Compounds



R	R_6	Therapeutic Index			References
		Canary	Java Sparrow	Siskin	
NH_2	OMe	16		13.9	12,24,234, 328,382
NH_2	OEt	16			13,382
NH_2	O-n-C_6H_9	8			13,14,382
NH-n-C_3H_7	OMe	8			14,382
NH-n-C_4H_9	OMe	8			14,382
NH-n-C_6H_9	OEt	<16			382
NH-n-C_6H_9	O-n-C_6H_9	4			14,382
NMe_2	OMe		10	16.5	118,234
NMe_2	OH		80		207P
NEt_2	Cl			2.5	234
NEt_2	Me	0			118
NEt_2	OH	40		18.5	118,207P,234
NEt_2	OMe	100		96.5	117,118,221, 243
NEt_2	OEt	4		4	117,221,242, 243
R_6*NHCH(CH_3)CH_2NEt_2	OMe	10		2	46,118,222, 234
N-Piperidyl	OEt			6	221,243

Table 16

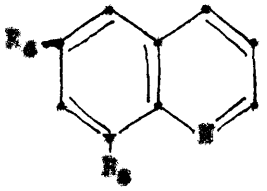
8-Aminobutylaminoquinoline Compounds



R_8	R_6	Therapeutic Index			References
		Canary	Java Sparrow	Siskin	
$NH(CH_2)_4NH_2$	OEt	30			13,269
$NH(CH_2)_4NEt_2$			10		118
$NH(CH_2)_4NEt_2$	OMe		10	10.6	99,118,210,222
$NH(CH_2)_4NEt_2$	OEt	16			269
$NHCH(Me)(CH_2)_3NMe_2$	OMe			++	58P,352P,356P,358P
$NHCH(Me)(CH_2)_3NEt_2$	OMe		10	25	117,222,234,352P

Table 17

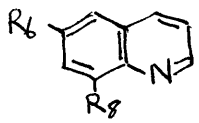
8-Aminopentylaminoquinoline Compounds



R_5	R_6	Therapeutic Index			References
		Canary	Java Sparrow	Siskin	
$NH(CH_2)_3NR_2$	OMe	1-10		+	19,24,234,302
$NH(CH_2)_3NHC_4H_9$	OMe	1			302
$NH(CH_2)_3NEt_2$			40		118
$NH(CH_2)_3NEt_2$	OMe		150	25	118,222,242, 243,352P
$NHCH(Me)(CH_2)_3NEt_2$	OMe	30,40,60	40	26.6	117,221,222, 239,243,352P
$NHCH_2C(Me)_2CH_2NMe_2$	OMe		40		117
$NHCH_2C(Me)_2CH_2NMe_2$	OEt		40		117,162P
$NHCH_2C(Me)_2CH_2NEt_2$	OMe		40	2	117,118,162P
$NHCH_2C(Me)_2CH_2NEt_2$	OEt		10		117,162P
$NHCH_2C(Me)_2CH_2NEt_2$	O-n-C_3H_7		10		117,162P
$NHCH_2C(Me)_2CH_2NEt_2$	O-n-C_4H_9		10+		117,162P
$NHCH(Et)(CH_2)_3NMe_2$	OMe		40		117
$NHCH(Et)(CH_2)_3NEt_2$	OMe		4		117,118

Table 18

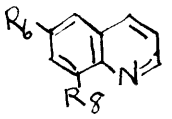
Higher 8-Aminoalkylaminoquinoline Compounds



R_6	R_8	Therapeutic Index Canary	Therapeutic Index Java Sparrow	Therapeutic Index Siskin	References
$NH(CH_2)_6NEt_2$	OMe		150	13.3	39,118,222,240
$NHCH(Me)(CH_2)_4NEt_2$	OMe			25	222
$NHCH_2CH(\underline{iso}\text{-}C_4H_9)NEt_2$	OMe		4*	4-5.3	117,221,235
$NHCH_2CH(\underline{iso}\text{-}C_4H_9)NEt_2$	OEt		0-4		115,117
$NH(CH_2)_7NEt_2$	OMe	1000	166	33.3	6,39,222,240
$NH(CH_2)_8NEt_2$	OMe	500	175		5F,6
$NH(CH_2)_9NEt_2$	OMe	700	180	40	5F,6,39,222,240
$NH(CH_2)_{11}NMe_2$	OMe	50			40
$NH(CH_2)_{11}NEt_2$		25			40
$NH(CH_2)_{11}NEt_2$	Me	0			40
$NH(CH_2)_{11}NEt_2$	OMe	100	10	5.0	39,40,118,222,240
$NHCH(Me)(CH_2)_9NEt_2$	OMe	125			40
$NH(CH_2)_9CH(Me)NEt_2$	OMe			0	222,240

Table 12

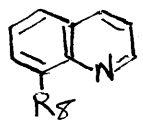
Effect of the Type of Side-Chain in Position 8



R_6	R_8	Therapeutic Index Host		References
$NH(CH_2)_3NH(CH_2)_2NEt_2$	OEt	++		328
$NH(CH_2)_2O(CH_2)_2NH_2$	OMe	8	Sparrow	14,382
$NH(CH_2)_3S(CH_2)_2NEt_2$	OMe	+		58P,59P,352P, 356P
$NHCH_2CHCHCH_2NEt_2$	OEt	15	Siskin	58P,243,352P, 356P,358P
$NHCH(CH_2OEt)CH_2NMe_2$	OMe	4+	Sparrow	117
$NHCH(CH_2OEt)CH_2NEt_2$	OMe	10	Sparrow	117
$NHCH(CH_2O\text{-}n\text{-}C_4H_9)CH_2NMe_2$	OMe	4	Sparrow	117
$NHCH(CH_2O\text{-}n\text{-}C_4H_9)CH_2NEt_2$	OMe	10	Sparrow	117
$NHCH(CH_2O\text{-}n\text{-}C_4H_9)CH_2NEt_2$	OEt	0	Sparrow	117
$NHCH(CH_2O\text{-}iso\text{-}C_5H_{11})CH_2NMe_2$	OMe	4	Sparrow	117
$NHCH(CH_2\text{-}C_6H_4\text{-}p\text{-}OMe)CH_2NMe_2$	OMe	10	Sparrow	117
$NH(CH_2)_2NH(CH_2)_2NEt_2$	OMe	++		328
$NH(CH_2)_3NH(CH_2)_3NH_2$	OMe	++		328
$NH(CH_2)_4NH(CH_2)_4NH_2$	OMe	++		50
$NH(CH_2)_2O(CH_2)_2NH(n\text{-}C_4H_9)$	OMe	8+	Sparrow	14,382
$NHCH(CH_2CH_2NEt_2)_2$. 5-O-iso-C_5H_7	OMe	++		328
$N(Et)(CH_2)_2NEt_2$	OMe	0		243
$CH_3NH(CH_2)_2NEt_2$		0		205
AsO_2NaR	OMe	±	Canary	115

Table 20

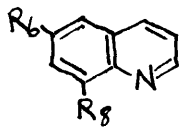
8-Heterocyclic quinolines



R_8	Other Groups	Therapeutic Index	References
2'-Pyridyl			19P
3'-Pyridyl			19P
$NHCH_2$-3'-(N-Me-piperidyl)	6-OMe		353P
$NH(CH_2)_3NH$-8'-(6'-Me-quinolyl)			13
$NH(CH_2)_3NH$-(2'-Me-4'-NH_2-8'-quinolyl)			108P
1'-Piperidyl	5-NO_2	-	199
NH-2'-(3'-Me-thiazolinyl)		0	45
$NH(CH_2)_2$-1'-piperidyl	6-OEt	6 Siskin	221,243
NHN-5'-[6'-OH-4'-CHOH-2"-(7"-Et-quinuclidyl)-quinolyl]	6-OMe 6-OEt 6-O-n-C_5H_{11}		191P 191P 191P
1'-Imidazolyl	6-OMe		95P,97
CH_2-1'-piperidyl			199
CH_2-1'-piperidyl-4'-CH_2-8'-quinolyl		0	205
$CH_2N(Me)(CH_2)_2N(Me)CH_2$-8'-quinolyl		0	205
CHOH-2'-(7'-Et-quinuclidyl)		0	336

Table 21

Miscellaneous 8-Quinolyl Derivatives



R_6	R_8	Therapeutic Index	References
NH_2	OH		242
NH_2	OMe	Canary 0; Sparrow 4+	115,117,157P,159P
NH_2	OEt	Canary 0; Sparrow <4	19,117,159P
NH_2	$O(CH_2)_2NH_2$		260
NH_2	$O(CH_2)_2NEt_2$	0	243
NH-n-C_6H_9; 5-NHCOCH$_3$	OMe		13
$NHCH_2CH{=}CH_2$			45
$NHNH_2$	OMe	Very slight	290
$NHCH_2NH_2$	OMe	0	24
NHCH(Me)CH_2OH	OEt		46
$NHCH_2CO_2Et$	OMe		328
$NH(CH_2)_3N{=}C(Me)CHCO_2$ (CH$_2$CH$_2$)	OMe		7P
$NHCH_2CONH_2$	OMe		44
$NHCH_2SC_6H_5$	OMe		47
$NHCH_2SC_6H_4$	OMe		47
$NHCOCH_2$-piperidyl	OMe	0	42
NHCOCHOHCH$_3$	OEt		46
NHCSNHCH$_2$CH=CH$_2$	OEt		45
$NHCO_2R$ (R=-Me,-Et, -n-C_3H_7, -n-C_4H_9, -iso-C_4H_9, -n-C_5H_{11}, -iso-C_5H_{11}, -n-C_6H_{13})		0	83

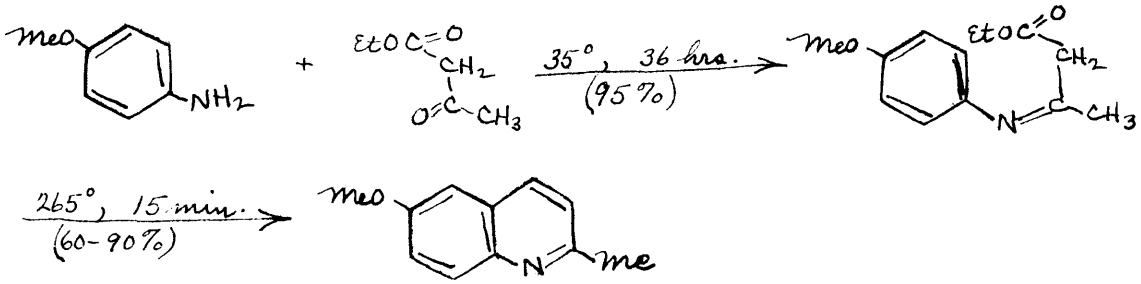
Table 21 (cont'd)

R_3	R_4	Therapeutic Index	References
$NHCONH_2$	OMe	±	36
OC_3H_7		0	146
OC_4H_9		0	146
$O(CH_2)_2NEt_2$	OMe	0	28,928
CH_2NEt_2			199
$CH_2NR(CH_2)_2NEt_2$ (R = -H, -Me, -Et, -n-C_3H_7, -n-C_4H_9, -iso-C_4H_9)		0	205
$CH_2NR(CH_2)_2$-piperidyl (R = -H, -Me, -Et, -n-C_3H_7, -n-C_4H_9, -iso-C_4H_9)		0	205
$CONH(CH_2)_2NEt_2$	OMe	0	340
$CO(CH_2)_2NEt_2$	OMe	0	340
$CO_2(CH_2)_2NEt_2$	OMe	0	340
AsO_3NaH		Canary ±; Human -	115

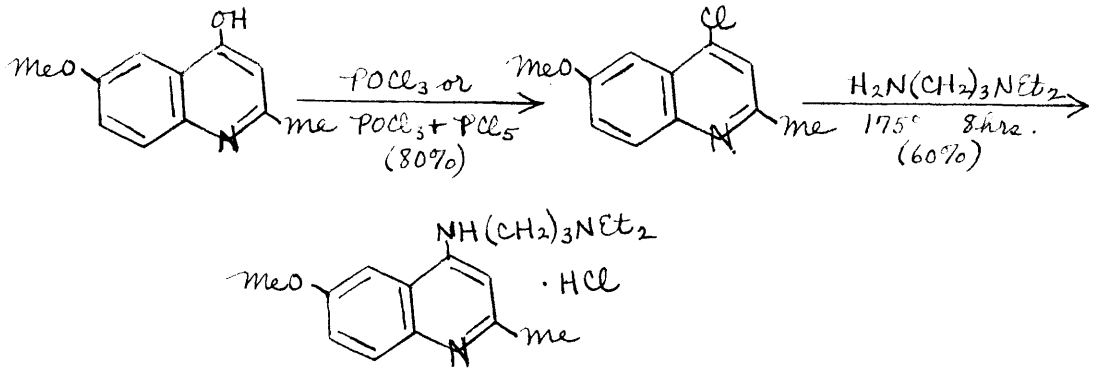
From the foregoing lists of compounds it may be seen that active 8-substituted quinoline derivatives possess the 8-sidechain attached to the nucleus through an -NH- group. The side-chain may be a straight or branched hydrocarbon, ether, thioether or amine and containing at least one other basic group, such as the dialkylamine group. A 6-methoxy group enhances the activity.

In the following tables, 72 through 91, are listed some of the quinoline derivatives which are substituted in positions 1 to 7. The only compounds which show any activity are those substituted in the 4-position. These 4-substituted quinoline derivatives are of two types, those which are 4-isomers of the plasmochin type and those which are 4-quinolyl carbinols -- resembling quinine.

Many of the 4-isomers of the plasmochin type are 4-amino substituted quinaldines, prepared by the Conrad-Limpach condensation:



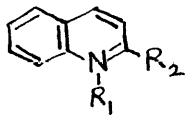
The 4-hydroxy-6-methoxyquinaldine is converted into the corresponding 4-chloro or 4-bromo derivative by treatment with phosphorous oxyhalide or a mixture of phosphorous oxyhalide and phosphorous pentahalide, and this compound is heated with the desired dialkylaminoalkylamine to yield the final product:



Many other syntheses of quinolines are described by Manske (252).

Table 22

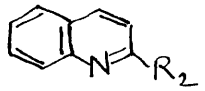
N-Substituted Quinoline Derivatives



R_1	R_2	Other Groups	References
$(CH_2)_2NH_2$, Cl		6-OH	362
$(CH_2)_2NH_2$, Cl		6-OMe	362
$(CH_2)_2NH_2$, Cl		6-OMe	362
$(CH_2)_2NH_2$	=O	6-OMe	362
$(CH_2)_2NEt_2$	2,3,4-H_2	6-OEt	169P
$(CH_2)_2NEt_2$	=O	4-$CONHC_6H_5$	376P
$(CH_2)_2N(C_6H_{11})_2$	=NH		34P

Table 2?

2-Substituted Quinoline Derivatives



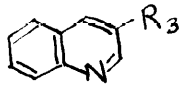
R_2	Other Groups	Activity	References
NEt_2	6-OMe	0	115
NEt_2	1-MeI		78,115
$NH(CH_2)_2NH_2$		0	115
$NH(CH_2)_2NEt_2$	1-MeI; 6-OMe	0	78
$NHCH_2CHCHCH_2NEt_2$	6-OMe	0	241
$NHCH_2CHCHCH_2NEt_2$	1-MeI	0	78
$NH(CH_2)_4NEt_2$	6-OMe	0	241
$NHCH(Me)(CH_2)_2NEt_2$	6-OMe	0	241
$NH(CH_2)_2OH_2$	4-Me		167P
NHC_6H_4-p-$(CH_2)_2NEt_2$	1-MeI; 6-OMe	0	78
$NH(CH_2)_2$-morpholinyl	4-Me; 6-NH_2		219
Piperidyl	4-OEt		48
Morpholinyl	4-OEt		48
Piperazyl		0	115
1'-[4'-$CH_2C(OH)(Me)(Et)$-piperazyl]		0	115
NHCONH-2'-quinolyl			342P
1'-Imidazolyl			95P,97
$(CH_2)_2NEt_2$			198
$(CH_2)_2NHMe$			175P
$(CH_2)_2$-pyridyl			232P

Table #3 (cont'd)

R_2	Other Groups	Activity	References
$(CH_2)_2NEt_2$	6-OMe		341P
$CH(Me)CH_2$-pyridyl			198
$(CH_2)_2NHSO_2$-C_6H_4-p-Me			175P
$CH=CH(CH_2)_2CH_2$	4-NH_2; 6-OEt		168P
$CH=CHCH=CHC_6H_5$	4-NH_2; 6-OEt		102P
C_6H_5	4-CO_2H; 6-Me		388P
C_6H_4-p-NH_2	4-CO_2H; 6-OMe	O	115
C_6H_4-o-C_6H_4-p-NHMe	6-SO_3H		388P
C_6H_4-p-O$(CH_2)_2NEt_2$			375P
C_6H_3-3',4',5'-$(CH)_3$	4-Me; 5-OH; 6-OH; 7-OH		388P
$CH=CHC_6H_5$	4-NEt_2; 6-OEt		162P
$CH=CHC_6H_4$-p-$NH(CH_2)_2NH_2$	6-OMe		261
-2'-(1'-OH-naphthyl)	6-OMe; 7-OMe		326
$O(CH_2)_2NEt_2$	3-C_6H_5		57P
$O(CH_2)_2NEt_2$	4-$O(CH_2)_2NEt_2$; 3-C_6H_5		375P
O-C_6H_3-3',4'-NH_2,OMe	4-Me		239

Table 24

3-Substituted quinoline Derivatives



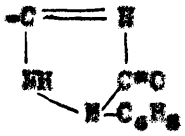
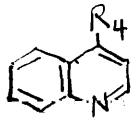
R_3	Other Groups	Activity	References
NH_2	1-EtI; 2-C_6H_5	+	193
NHCOCH-3'-(2'-Me-quinolyl)	2-Me		342P
NHCOCH=CHCONH-3'-(2'-Me-4'-NH_2-quinolyl)	2-Me; 3-NH_2; 4-NH_2		184P
NHCSNH-3'-(2'-Me-quinolyl)	2-Me		342P
	2-Me; 4-Me		126
$(CH_2)_3NEt_2$	6-Me		198
$CO(CH_2)_3NEt_2$	6-OMe	O	340
$COCH_2$-piperidyl	6-Me		198
$CHCHCH_2NEt_2$	2-OMe	O	291
CHCH-3'-(3'-Et-quinuclidyl)	2-OMe	O	291

Table 25

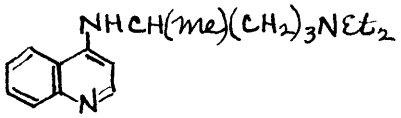
4-Substituted Quinoline Derivatives



R_4	Other Groups	Therapeutic Index	Host	References
NH_2	2-C_6H_5; 6-EtO	+	Canary	199
NHEt	2-C_6H_5; 6-MeO	-		114
NMe_2	2-Me; 6-MeO; 7-MeO			280
NEt_2	2-C_6H_5; 6-MeO	-		114
NHCOMe	2-C_6H_5	+		199
$NH(CH_2)_2NEt_2$				404P,405P
$NH(CH_2)_2NEt_2$	7-Cl	+		8P,9P
$NH(CH_2)_2$-piperidyl	7-Cl	+		8P,9P
$NH(CH_2)_2$-piperidyl	2-Me; 6-MeO			201
$NH(CH_2)_3NEt_2$	2-Me; 6-MeO	0, +		151,222
$NHCH_2CHOHCH_2NEt_2$				404P
$NHCH_2CHOHCH_2NEt_2$	6-MeO	3.3	Siskin	141,183
$NHCH_2CHOHCH_2NEt_2$	2-Me; 6-MeO	0		45
$NH(CH_2)_4NEt_2$	6-MeO	?	Siskin	141,183
$NH(CH_2)_4NEt_2$	7-Cl	+		8P,9P
$NHCH(Me)(CH_2)_2NEt_2$	6-OMe	+	Siskin	141

Table 26

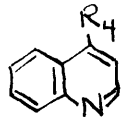
4-(δ-Diethylamino-α-methylbutyl)-aminoquinoline Derivatives



Other Groups	Therapeutic Index Rank		References
2-Me	+, 0		151,404P,405P
3-Me; 7-Cl			8P,9P
3-Me; 7-Br			8P,9P
3-Me; 7-I			8P,9P
3-Me; 5-Cl; 7-Cl			8P,9P
3-Me; 6-MeO; 7-Cl			8P,9P
3-Me; 5-Me; 6-Me; 7-Me			8P,9P
6-Me; 7-Me			8P,9P
6-Me; 7-Cl			8P,9P
7-Me			8P,9P
6-MeO	9	Siskim	141,241
7-MeO			8P
3-EtO; 7-Cl			8P,9P
5-Cl; 7-Cl			8P,9P
6-Cl; 7-Cl			8P,9P
7-Cl			8P,9P
7-I			8P,9P
7-CF_3			8P
3-C_6H_5; 7-Cl			8P,9P
3-C_6H_5; 5-Cl; 7-Cl			8P

Table 27

4-Substituted Quinoline Derivatives



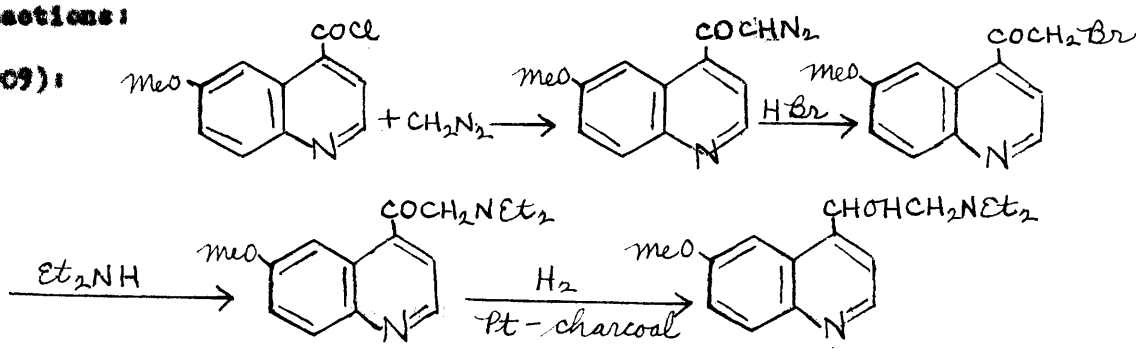
R_4	Other Groups	Activity	Host	References
Piperidyl	2-Me, 6-OMe			126
Morpholinyl	2-Me, 6-OMe			96
Piperazyl	2-Me, 6-OMe			200
NH-6′-quinolyl	2-Me, 6-OMe			151
$NH(CH_2)_3O(CH_2)_2NEt_2$	7-Cl	+		8P,9P
$NH(CH_2)_3O(CH_2)_2NEt_2$	6-OEt			59P
$NH(CH_2)_3S(CH_2)_2NEt_2$	7-Cl			8P,9P
NHC_6H_4-p-OMe	2-Me, 6-OMe	0		12
NHC_6H_4-p-SO_2NH_2				33
$CH_2NH(CH_2)_2NEt_2$	6-OMe	0		340
$(CH_2)_2NH_2$	2-Me, 6-OMe, 7-OMe			280
$(CH_2)_2NMe_2$				292P
$(CH_2)_2CO_2(CH_2)_2NEt_2$	2-Me, 6-OMe, 7-OMe			326
CO_2H	2-C_6H_5, 3-Et	0		228
CO_2Et	2-Me	0	Canary	115
CO_2Et	2-C_6H_4-p-NH_2	0	Canary	115,116
$CO_2(CH_2)_2NEt_2$	2-C_6H_5	0		399P
$CONEt_2$	2-Et, 3-Me	0		228
CONH-6′-quinolyl	2-Me			342P
$CO(CH_2)_2NEt_2$	6-OMe	-		340
$CO(CH_2)_2NHMe$	6-OMe	0		337
$O(CH_2)_2NH_2$	2-Me, 6-OMe			326

Table 27 (cont'd)

R_5	Other Groups	Activity	Heat	References
OC_6H_5	2-Me, 6-Et			231
OC_6H_4-p-OMe	2-Me, 6-Et			231
OC_6H_3-p,m-(Me)(NH_2)	2-Me			195
OC_6H_3-p,m-(OMe)(NH_2)	2-Me, 6-Et			231

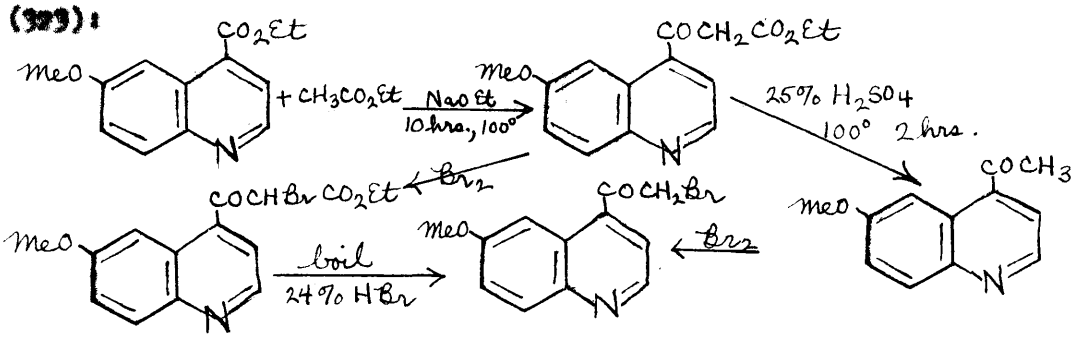
The 4-quinolyl carbinols have been prepared by the following reactions:

(209):



The bromoethyl ketone may be prepared by the following reactions:

(399):



The methyl ketone may be prepared in good yield from the nitrile.

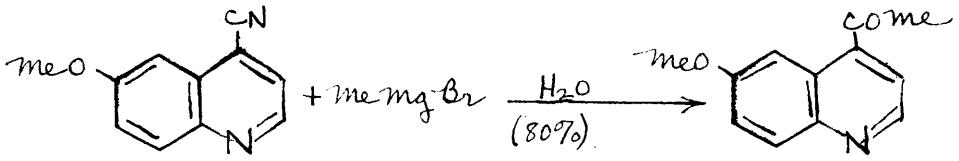
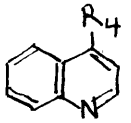


Table 26

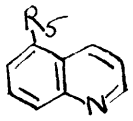
Substituted 4-Quinolyl Carbinols



R_4	R_2	Activity	Host	References
$CHOHCH_2NH_2$	OMe			340
$CHOHCH_2NEt_2$	OMe	-	Canary	209
$CHOHCH_2NEt_2$	OEt			197
$CHOHCH_2N(n\text{-}C_4H_9)_2$	OMe	+	Canary	209
$CHOHCH_2N(n\text{-}C_5H_{11})_2$	OMe	+	Canary	209
$CHOHCH_2N(iso\text{-}C_5H_{11})_2$	OMe	0	Canary	209
$CHOHCH_2N(n\text{-}C_6H_{13})_2$	OMe	+	Canary	209
$CHOHCH_2N(n\text{-}C_7H_{15})_2$	OMe	0	Canary	209
$CHOHCH_2$-piperidyl		0 , +		197,209,323
$CHOHCH_2$-piperidyl	OMe	slight	Canary	209,323
CHOH-2'-pyrryl		0		195
CHOH-2'-pyrryl	OMe	slight		195
CHOH-2'-pyrryl	OEt	0		195
CHOH-2'-piperidyl		0		4
CHOH-2'-piperidyl	OMe	1/2 Q.E.		4
CHOH-2'-piperidyl	OEt	1/2 Q.E.		4
CHOH-2'-(1'-Me-piperidyl)	OMe	0		4
CHOH-2'-(1'-Pr-piperidyl)	OMe	0		4
CHOH-2'-(1'-Bu-piperidyl)	OMe	0		4
$CHOH(CH_2)_2$-4'-(3'-Et-piperidyl)	OMe	0		319
CHOH-2'-quinuclidyl	OMe	+, 0, (?)		313,318
CHOH-2'-(1'-CH_2=$CHCH_2$-piperidyl)		0		4
CHOH-2'-(1'-CH_2=$CHCH_2$-piperidyl)	OMe	0		4
CHOH-2'-(1'-CH_2CH=$CHCH_2$-piperidyl)		0		4
CHOH-2'-(1'-CH_2CH=$CHCH_2$-piperidyl)	OMe	0		4
$CHOHCH_2$-1'- 4'-(4"-piperidyl)-piperidyl		0		209
$CHOHCH_2$-1'- 4'-(4"-piperidyl)-piperidyl	OMe	slight		209

Table 22

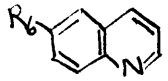
5-Substituted Quinoline Derivatives



R_5	Other Groups	Activity	Host	References
$NH(CH_2)_2NH_2$	8-NH_2	0	Canary	115,116
$NH(CH_2)_2NH_2$	6-OMe, 8-NO_2	0	Canary	115,116
2'-Pyridyl	8-OMe			19P
NHCONH-4'-(3'-Me-quinolyl)	6-OMe			342P
N=N-6'-(2'-Me-4'-NH_2-quinolyl)	2-Me, 4-NH_2, 6-NH_2			178P
N=N-3'[2',6'-$(NH_2)_2$-pyridyl	2-Me, 4-NH_2			178P
N=N-4'-(1'-C_6H_3-2'-Me,Cl-3'-Me-5'-CH-pyrazolyl)	2-Me, 4-NH_2			178P
$NHSO_2$-C_6H_4-p-NH_2				33
$CO_2(CH_2)_2NEt_2$	8-OMe			340

Table 30

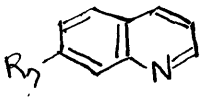
6-Substituted Quinoline Derivatives



R_6	Other Groups	Activity	Host	References
NH_2	8-OMe	0		115
$NH(CH_2)_2NH_2$	5-NH_2	0	Canary	115
$NH(CH_2)_2NEt_2$	8-OMe	0.<4		115,117
$NHCH_2SO_3Na$				47
2'-Pyridyl				19P
3'-Pyridyl				19P
4'-Pyridyl				19P
NH-2'-[4',6'-$(NH_2)_2$-sym-triazinyl]	2-Me, 4-NH_2			187P
NH-2'-[4'-$NH(CH_2)_2NEt_2$-6'-NH-6"-(2"-Me-4"-NH-quinolyl-sym-triazinyl]	2-Me, 4-NH_2			177P,187P
NHCONH-C_6H_4-p-O-C_6H_3-3,5-$(Me)_2$				342P
NHCONH-C_6H_4-p-$O(CH_2)_2NEt$				342P
NHCSNH-6'-quinolyl				342P
NHC(=NH)NH-6'-quinolyl				342P
NHCOCH=CHC_6H_5	2-Me, 3-NH_2, 4-NH_2			184P
NHCOCH=CHCONH-6'-(2'-Me-4'-NH_2-quinolyl)	2-Me, 4-NH_2			187P
NHCS-C_6H_3-3',4'-$(NO_2)(Me)$				343P
N=N-C_6H_4-p-$(CH_2)_2NEt_2$	2-Me, 4-NH_2			178P
Me	2-Br, 4-NO_2	-		205
$(CH_2)_2NEt_2$		-		340
CH		-	Canary	146
OC_6H_7-n		-	Canary	146
$O(CH_2)_2NEt_2$	8-N(COC_6H_5)Et			243
$O(CH_2)_2NMe_2$	8-NH_2			260
$O(CH_2)_2O$-6'-(2'-Me-4'-NH_2-quinolyl)	2-Me, 4-NH_2			189P
$OCH_2CHOHCH_2O$-6'-(2'-Me-4'-NMe_2-quinolyl)	2-Me, 4-NMe_2			189P
$O(CH_2)_2$-1'-piperazino-4'-$(CH_2)_2O$-6'-(2"-Me-4"-NH_2-quinolyl)	2-Me, 4-NH_2			189P

Table 31

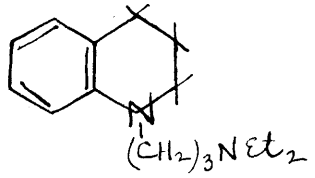
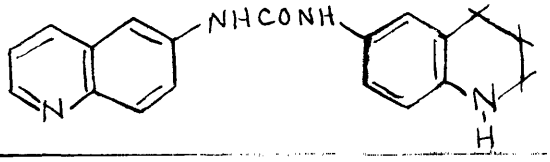
7-Substituted Quinoline Compounds



R_7	Other Groups	Activity	Host	References
$NH(CH_2)_2NH_2$		0		115
$NH(CH_2)_2NH_2$	8-NH_2	0	Canary	115
NHCONH-7'-quinolyl				342P
NHCSNH-7'-quinolyl				342P
NHCO-C_6H_3-4'-Me-3'-NHCH(CH_3)-$(CH_2)_2NEt_2$				349P
$O(CH_2)_2NEt_2$	2-C_6H_5			375P
AsO_3HNH	8-NO_2	0	Canary	115

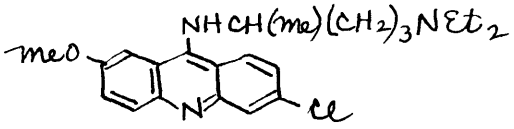
Table 32

Tetrahydroquinoline Compounds

Structure	Reference
	400
	342P

Acridine Derivatives

The second largest group of synthetic antimalarials are derivatives of the acridine series. Since active antimalarial agents had been produced by substitution of dialkylaminoalkylamino groups in 6-methoxyquinoline, it was only natural that substitution of similar chains in other nuclei was attempted, ultimately resulting in the production of atabrine (XI), the first schizonticidal drug, by Mauss and Mietzsch (265, 277), assisted by Kikuth (206) in the biological work.

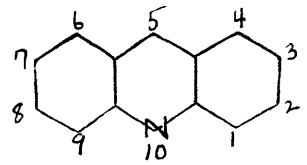


(XI)

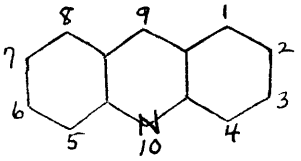
It is not surprising that acridine derivatives should prove to be effective antimalarials for they may be considered to be 2,3-benzoquinolines and hence have a certain similarity. Just as in the case of the quinoline derivatives it is found in the acridine series that so long as the position and type of side-chain is maintained, it can be altered considerably and still produce active compounds. The groups in positions 2 and 6 may be varied and produce effective antimalarials.

The schizonticidal drug atabrine compares favorably with quinine and is being used extensively in the treatment of malaria, both in civil practice and in military medicine.

There has been much confusion about the numbering of acridine compounds. Formula XII shows the numbering used by the English, French, and Chemical Abstracts before 1937; and formula XIII shows that used by the Germans, Russians, Chemical Abstracts since 1937, and used in this paper.



XII

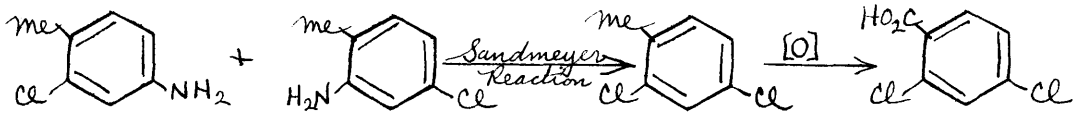


XIII

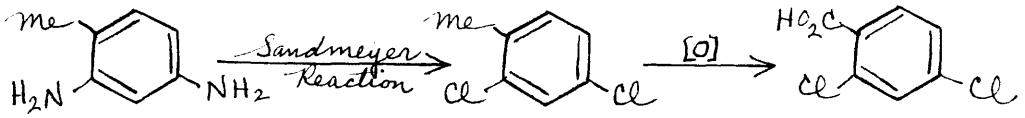
Atabrine is manufactured in the United States by the Winthrop Chemical Company, Inc. under U. S. P. 2,113,357 (2787), and according to Ehorndal (969) the process involves the following steps.

1. Preparation of 2,4-dichlorobenzoic acid:

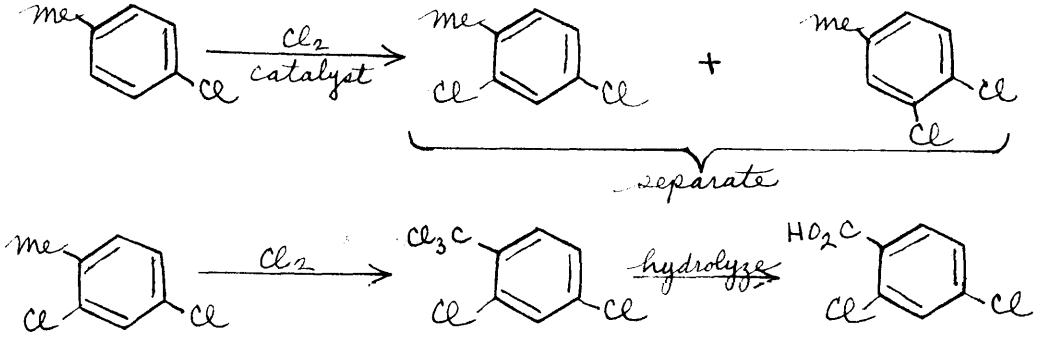
a. Major method until 1943:



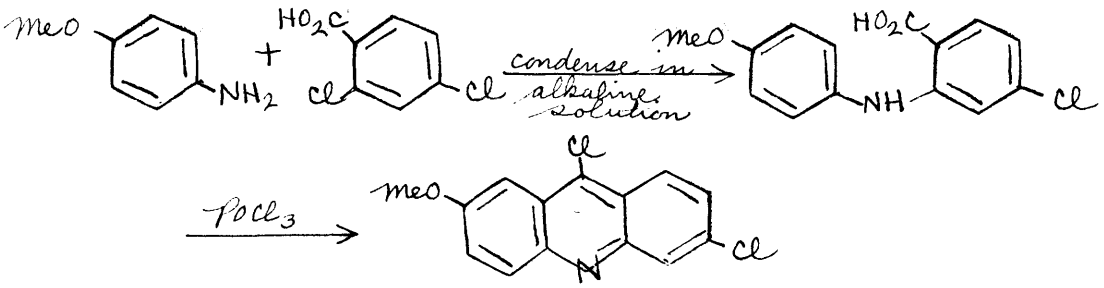
b. Minor method until 1943:



c. New method which accounts for much of the 1943 production:



2. Preparation of 9-methoxy-6,9-dichloroacridine:



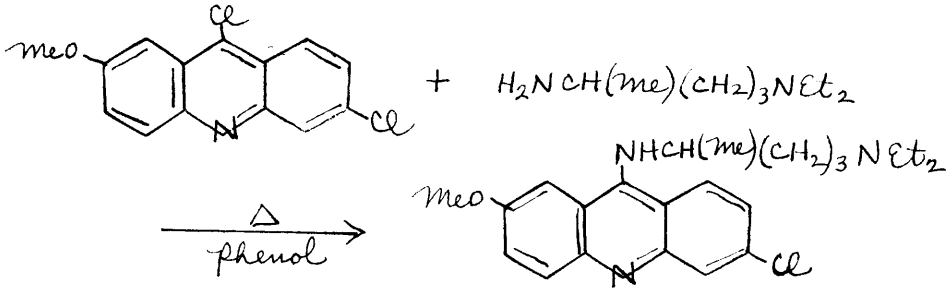
3. Preparation of δ-diethylaminoisopentylamine:

$$Et_2N(CH_2)_3OH \xrightarrow{SOCl_2} Et_2N(CH_2)_3Cl$$

$$Et_2N(CH_2)_3Cl + (CH_3COCHCO_2Et)Na \longrightarrow CH_3COCHCO_2Et \quad (CH_2)_3NEt_2 \text{ (not isolated)}$$

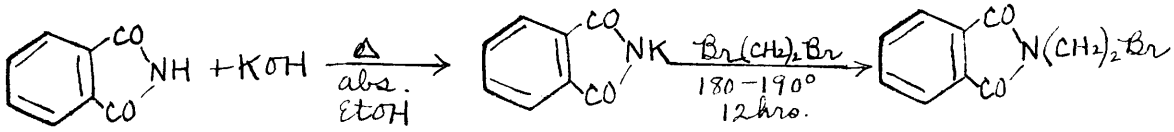
$$\xrightarrow[H_2SO_4]{H_2O} CH_3CO(CH_2)_3NEt_2 \xrightarrow[\text{Catalyst}]{H_2} H_2NCH(Me)(CH_2)_3NEt_2$$

4. Preparation of 2-methoxy-6-chloro-9-(δ-diethylaminoisopentylamino)-acridine:

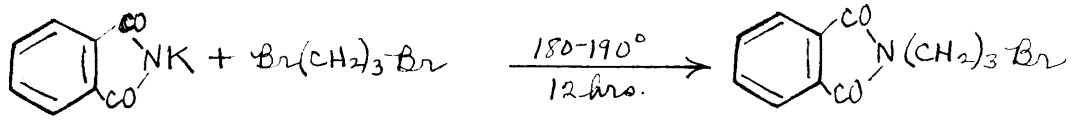


The dialkylaminoalkylamines used in synthesising acridine derivatives may be prepared by means of several methods. The Gabriel phthalimide synthesis (129) involves the reaction of an alkylene dihalide with potassium phthalimide, or phthalimide and potassium carbonate, to produce a phthalimide alkyl halide.

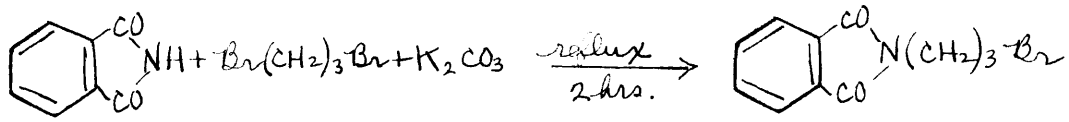
(900):



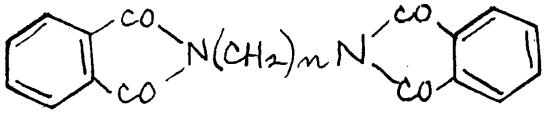
(92, 758):



(181):



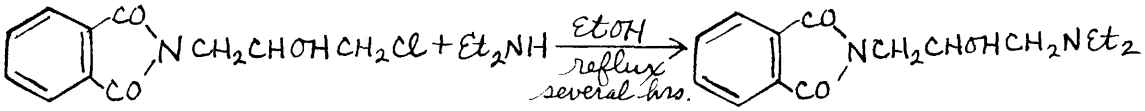
The yield in this step of the reaction is not high due to the formation of a diphthalimidoalkane as a result of the reaction of two moles of phthalimide with one mole of alkylene dihalide.



The phthalimide alkyl halide is next reacted with a secondary amine to produce a phthalimidoalkyldialkylamine.

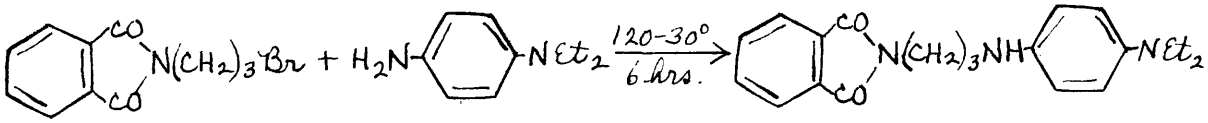
(32, 298)

(161P, 186P):



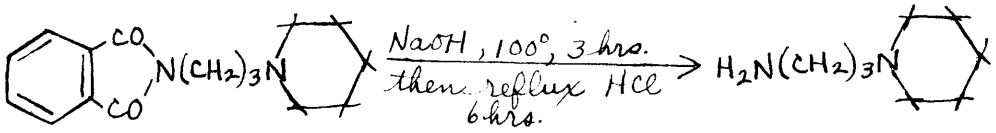
With a primary amine:

(49):

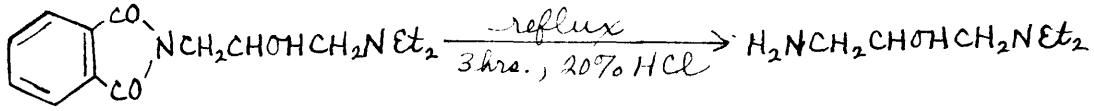


The phthalimidoalkylamine is finally hydrolyzed to produce a dialkylamino-alkylamine. The hydrolysis is accomplished by boiling with alkali and/or acid, or according to more recent methods, by treatment with hydrazine hydrate.

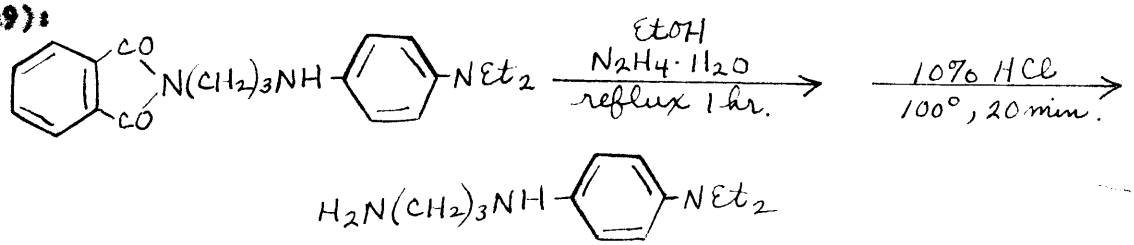
(32, 298):



(161P, 186P):



(49):



Recently a method has been described by Holcomb and Hamilton (151) for the production of dialkylaminopropylamines by reacting acrylonitrile with a secondary amine. A dialkylaminopropionitrile is formed and this compound is reduced by means of hydrogen and Raney nickel to the desired compound.

(151):

$$CH_2{=}CHCN + (n\text{-}C_5H_{11})_2NH \xrightarrow[(90\%)]{50^\circ} (n\text{-}C_5H_{11})_2N(CH_2)_2CN$$

$$\xrightarrow[\text{Raney Ni (47\%)}]{H_2} (n\text{-}C_5H_{11})_2N(CH_2)_3NH_2$$

(49):

$$CH_2{=}CHCN + \left[CH_3(CH_2)_3CH(Et)CH_2\right]_2NH \xrightarrow[100\text{ hrs.}]{100^\circ} \left[CH_3(CH_2)_3CH(Et)CH_2\right]_2\text{-}$$

$$N(CH_2)_2CN \xrightarrow[\text{Raney Ni}]{H_2} \left[CH_3(CH_2)_3CH(Et)CH_2\right]_2N(CH_2)_3NH_2$$

To decrease the formation of the byproduct secondary amine during the reduction, the nitrile is saturated with ammonia under pressure prior to reduction.

$$2\ R_2N(CH_2)_2CN \xrightarrow{H} \left[R_2N(CH_2)_3\right]_2NH + NH_3$$

A dialkylaminobutyronitrile can be prepared from ethyl cyanoacetate.

(107):

$$Na(CHCHCO_2Et) + Cl(CH_2)_2NEt_2 \xrightarrow[1\text{ hr.}]{\text{reflux}} CHCH(CO_2Et)(CH_2)_2NEt_2$$

The aminoester is catalytically reduced and then the carbethoxy group is removed by hydrolysis followed by decarboxylation.

$$CHCH(CO_2Et)(CH_2)_2NEt_2 \xrightarrow[\text{Raney Ni}]{H_2} H_2NCH_2CH(CO_2Et)(CH_2)_2NEt_2$$

$$\xrightarrow{(HCH)} H_2NCH_2CH(CO_2H)(CH_2)_2NEt_2 \xrightarrow{\Delta} H_2N(CH_2)_4NEt_2$$

Many dialkylaminoalkylamines may be prepared from dialkylaminoketones. The dialkylaminoketone is converted to the oxime and then reduced with sodium and an alcohol, or by catalytic means. The aminoketone can be converted directly to the diaminoalkane by catalytic reduction in the presence of ammonia. The Mannich reaction is used to prepare amino ketones of the type: $RCOCHR'CH_2NR''_2$, and aminoaldehydes of the type $R''_2NCH_2CR'_2CHO$.

(94):

$$CH_3COCH_3 + HCHO + Et_2NH.HCl \xrightarrow[(66\%)]{} CH_3CO(CH_2)_2NEt_2$$

(250):

$$CH_3COCH_2Et + HCHO + Me_2NH.HCl \longrightarrow CH_3COCH(Et)CH_2NMe_2$$

(50,251)

$$Me_2CHCHO + HCHO + Me_2NH.HCl \xrightarrow[(70\text{-}80\%)]{} Me_2NCH_2C(Me)_2CHO$$

β-Keto esters have been used to prepare dialkylaminoketones.

(107F, 239, 363):

$$Na(CH_3COCHCO_2Et) + Et_2N(CH_2)_2Cl \longrightarrow CH_3COCH(CO_2Et)(CH_2)_2NEt_2$$
$$\xrightarrow{10\%\ H_2SO_4} CH_3CO(CH_2)_2NEt_2$$

(197):

$$Na(CH_3COCRCO_2Et) + Et_2N(CH_2)_2Cl \longrightarrow CH_3COCR(CO_2Et)(CH_2)_2NEt_2$$
$$\longrightarrow CH_3COCHR(CH_2)_2NEt_2 \quad \text{where R} = CH_3^-,\ C_2H_5^-,\ \underline{\text{iso}}\text{-}C_3H_7^-$$

The dialkylaminoketone can be prepared by reacting a haloketone with a secondary amine. Several methods are available for preparing the haloketone.

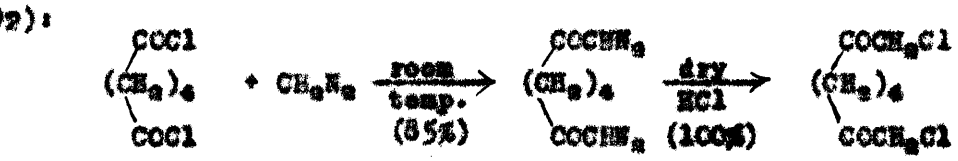
a. Bromination of ketones with α-hydrogen atoms:

(306): $$CH_3COCH_3 + Br_2 \xrightarrow[(43\text{-}45\%)]{} CH_3COCH_2Br$$

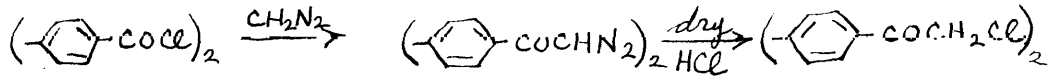
(309): $$C_6H_5COCH_3 + Br_2 \xrightarrow[(74\text{-}80\%)]{} C_6H_5COCH_2Br$$

b. Wierenstein reaction (220, 221):

(392):

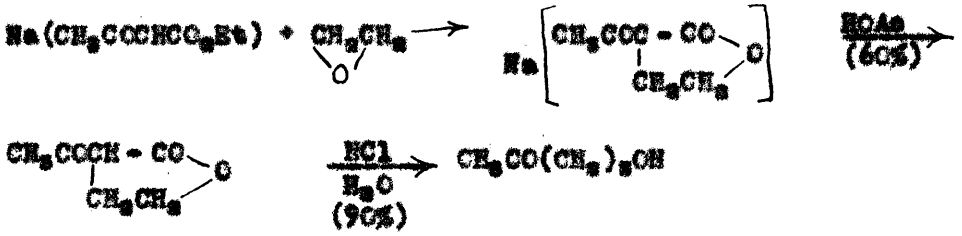


(400):



c. Halogenation of a hydroxyketone:

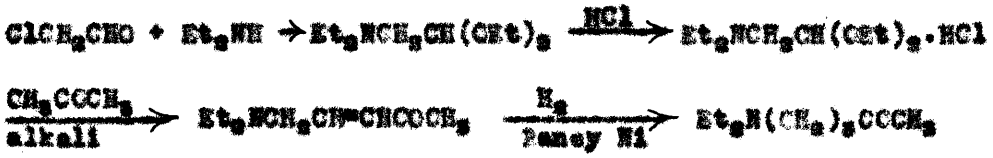
(140, 216, 217):



(216):

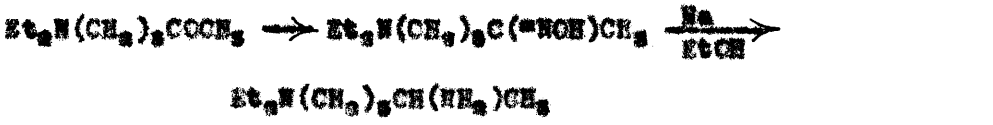
d. Miscellaneous:

(198):

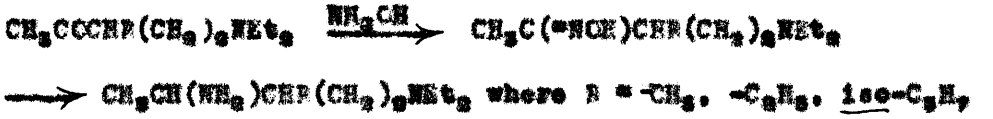


The dialkylaminoketone is then converted, either through the oxime, or by reduction in the presence of ammonia, to the dialkylaminoalkylamine.

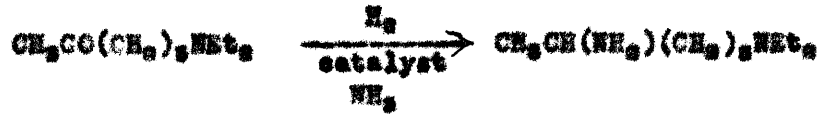
(216, 239):



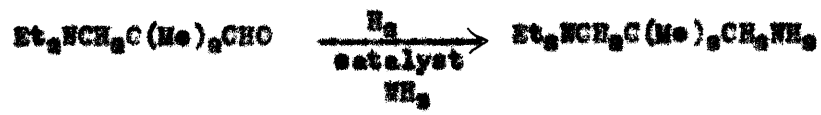
(197):



(369):

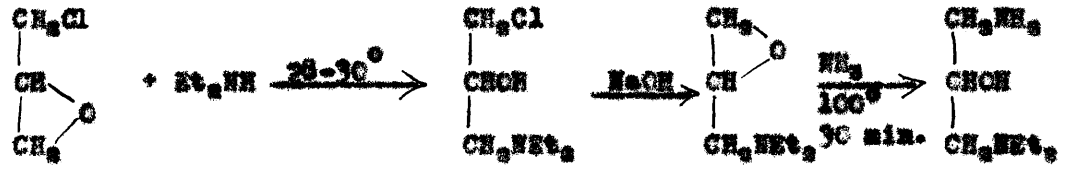


A dialkylaminoaldehyde can be treated similarly:



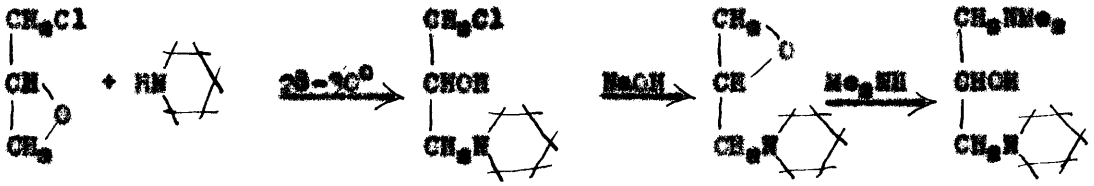
Dialkylaminoalkylamines can be readily prepared from epichlorohydrin.

(106P):



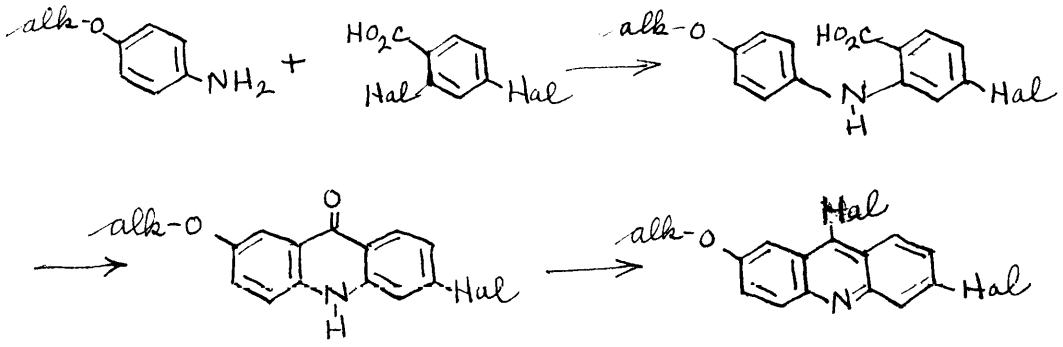
This synthesis can be utilized to prepare di-dialkylamino alkanols.

(101P):

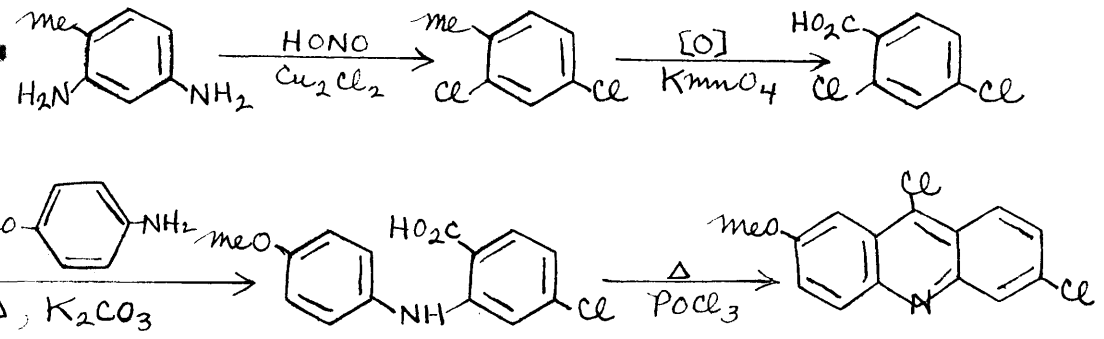


The synthesis of the acridine nucleus is illustrated by several examples below:

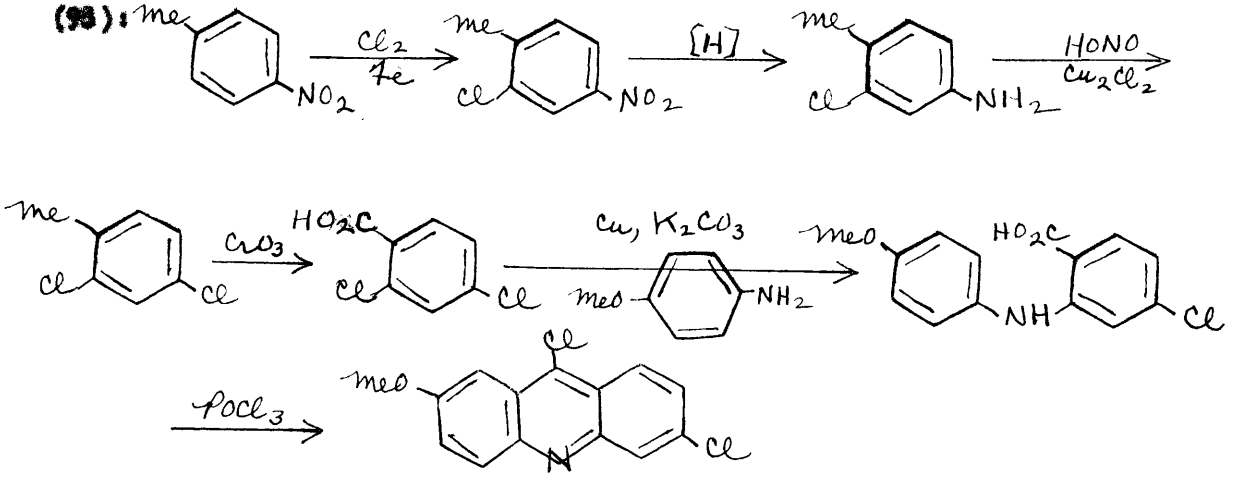
(96?P):



(216):

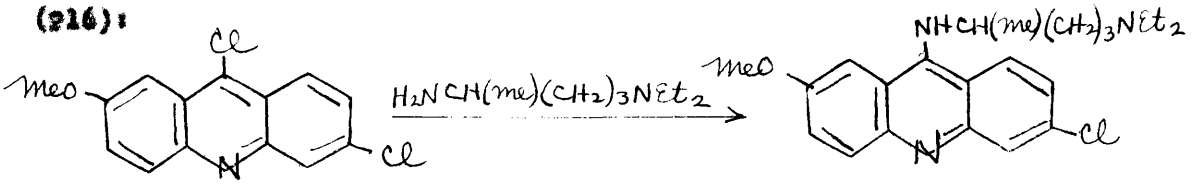


(98):

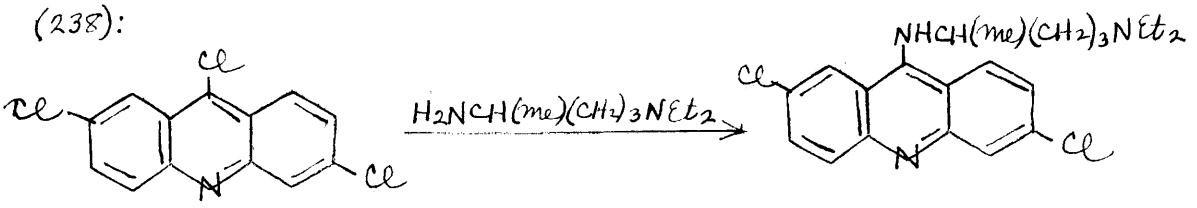


The substituted 9-chloroacridine is condensed with the dialkylaminoalkylamine by heating in the presence of phenol.

(216):

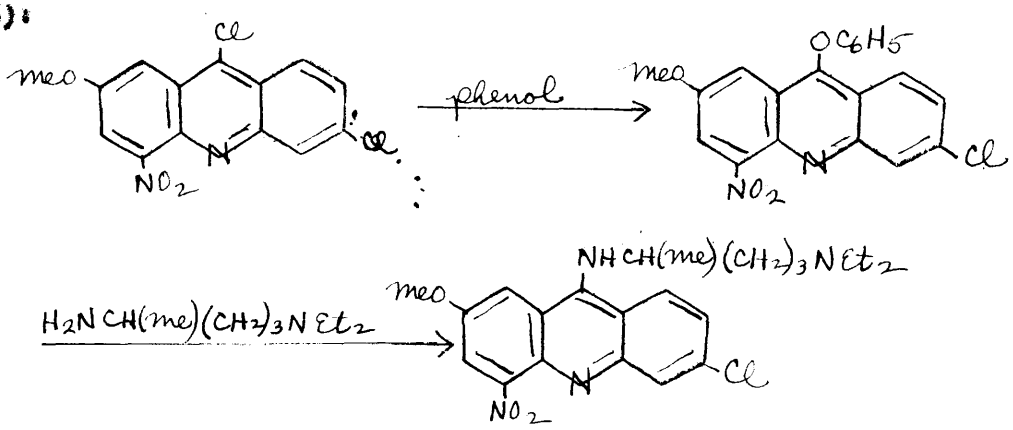


(238):

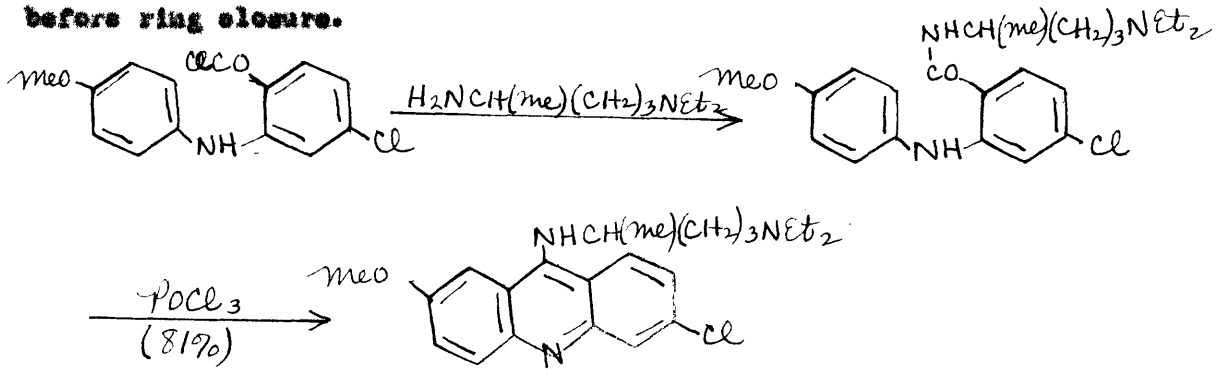


Only the 9-chloro atom is active since no compound is obtained with the side-chain in any other position. If the phenol is omitted the yield of condensation product is small; the 9-phenoxy derivative has been shown to be an intermediate in the reaction.

(215):



Drozdov (91) has condensed the amine with the intermediate acid chloride before ring closure.

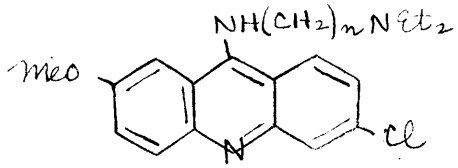
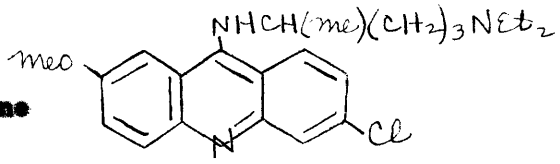


Nearly all of the antimalarials related to acridine are substituted 9-amino derivatives. An increase in the length of the dialkylaminoalkylamino side-chain in compounds related to Atabrine effects at first an increase and then a decrease in the therapeutic index. In contrast to the Plasmochin series there is no change in the therapeutic index for even and odd carbon chains. While the lower members are more active, they are also more toxic, and the compound with optimum relation between activity and toxicity is the C_4 compound. The effect of branching in the side-chain is strikingly shown when the amyl isomers are compared. Atabrine is more than twice as effective as the n-amyl isomer; however the n-butyl compound is more than three times as effective as the iso-butyl compound, while both the n-hexyl and iso-hexyl isomers have the same indices.

The therapeutic index of acridine derivatives have been determined in nearly every case by tests on Siskins infected with Plasmodium praecox.

Table 73

Effect of the Length of the Alkylamine Side-Chain in the 2-Methoxy-6-Chloro-9-Aminoacridines

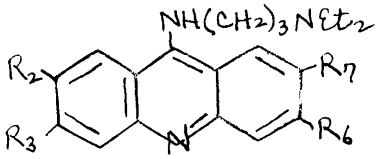
n	Therapeutic Index	
2	7.5	
3	15	
4	20	
5	6	
6	5	
2	6.6	
3	15	Atabrine
4	5	

References: 220, 222, 237

It may be seen from the data presented in Tables 74 and 75 that the 2-methoxy derivatives are inactive. Introduction into the 2-methoxy derivatives of a chloro or cyano group in the 6-position, or of a chloro or nitro group in the 7-position produces active compounds. The 6-nitro compound, however, is inactive. Substitution of a chloro group in the 6-position produces a more active compound than in the 7-position. The introduction into the 2-methoxy-6- or 7-chloro derivatives of a methoxy group has a diatherapeutic effect, producing inactive compounds. Whereas in the quinoline series the replacement of the methoxy group with a methyl group produces an inactive compound, in the acridine series the compound is active, but to a lesser degree.

Table 24

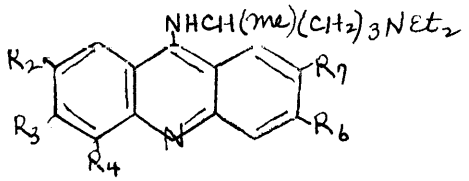
Effect of Substituents on the Antimalarial Activity of 9-(γ-Diethylaminopropylamino)-acridine



R_2	R_3	R_6	R_7	Therapeutic Index	References
OMe				0	237
OMe		Cl		15	237
OEt		Cl		7.5	237
Me		Cl		6	237
OMe		CN		10	245
SMe		Cl		2.8	245
OMe			Cl	?	110,222
OMe			NO_2	2.5	237
OMe	OMe	Cl		0	237
OMe	OMe		Cl	0	237

Table 25

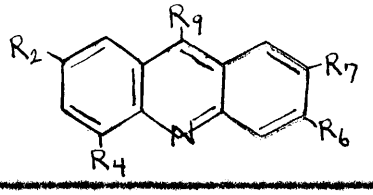
Effect of Substituents on the Antimalarial Activity of 9-(δ-Diethylamino-α-methylbutylamino)-acridine



R_2	R_3	R_4	R_6	R_7	Therapeutic Index	References
OMe					0, +	69,110
OMe			Cl		15	237,239
OMe			CN		23	245
NMe_2			Cl		+	63
OMe				Cl	2	222
OMe				NO_2	4	237
OMe	OMe		Cl		0	222,237
OMe			Cl	Cl	6	110
OMe		NO_2	Cl		slight	215
OMe		NH_2			0	215
OMe	OMe			Cl	0	222,237

Table 36

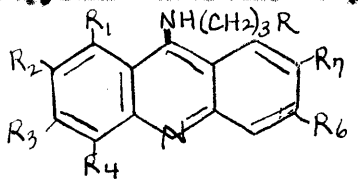
9-Aminoethylaminoacridine Compounds



R_2	R_6	Other Groups	Activity	References
$NH(CH_2)_2NMe_2$				202
$NH(CH_2)_2NEt_2$				134P
$NH(CH_2)_2$-piperidyl				134P,202
$NH(CH_2)_2NHC_6H_5$				134P
$N(Et)(CH_2)_2NEt_2$				348P,352P,356P, 358P
$NH(CH_2)_2NEt_2$	Cl			274P
$NH(CH_2)_2NEt_2$	OMe			135
$N(Me)(CH_2)_2NEt_2$	OMe			135
$NH(CH_2)_2NEt_2$	OEt			237
$NH(CH_2)_2NEt_2$	Cl	4-Cl		135
$NH(CH_2)_2NEt_2$	Me	4-Br		135
$NH(CH_2)_2NEt_2$	OMe	6-Cl	7.5	237,263P,266P
$NH(CH_2)_2NEt_2$	OMe	$6-NO_2$		237,263P
$NH(CH_2)_2NEt_2$	OMe	$6-NH_2$		263P
$NH(CH_2)_2NEt_2$	OEt	6-Cl		237,263P
$NH(CH_2)_2NEt_2$	OEt	$6-NO_2$		21,201
$NH(CH_2)_2NEt_2$	OEt	$7-NO_2$	1.5	237
$NH(CH_2)_2$-piperidyl	OMe	6-Cl		263P
$NH(CH_2)_2NMe_2$	OMe	7-OMe		279P

Table 37

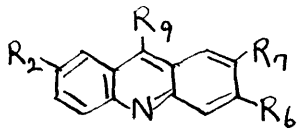
9-Aminopropylaminoacridine Compounds



R	R_n	Other Groups	Activity	References
NEt_2			0	237
NEt_2	OMe		0	195,237
NEt_2	OEt		+	237
NMe_2	OMe	6-Cl		263P
NEt_2	Cl			274P
NEt_2		1-Cl, 4-Cl		195
NEt_2	Cl	4-Cl		195
NEt_2	Me	4-Br		195
NEt_2	Me	6-Cl	6	222,237
NEt_2	OMe	6-Cl	15	220,222,237,263P
NEt_2	OMe	6-CN	10	237
NEt_2	OEt	6-Cl	7.5	222,237
NEt_2	OEt	6-NO_2	+,0	237
NEt_2	SMe	6-Cl	9.8	245
NEt_2	SMe	6-CN	2	237
NEt_2	SEt	6-Cl		273P
NEt_2	OMe	7-Cl	2	110,222,237,263P
NEt_2	OMe	7-Br		263P
NEt_2	OMe	7-I		263P
NEt_2	OMe	7-NO_2	2.5	222,237
NEt_2	OEt	7-NO_2	+	237
NEt_2	Cl	4-Cl, 7-Cl		195
NEt_2	OMe	3-OMe, 6-Cl	0	222,237
NEt_2	OMe	6-Cl, 7-NO_2		238
NEt_2	OEt	6-NO_2, 7-NO_2		237
Morpholinyl	OMe	6-Cl	0	238
Piperidyl				274P
Piperidyl	OMe	7-OMe		275P

Table 38

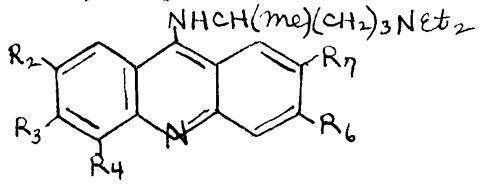
9-Aminobutylaminoacridine Compounds



R_2	R_6	Other Groups	Activity	References
$NH(CH_2)_4NEt_2$	Cl			274P
$NH(CH_2)_4NEt_2$	OMe			20
$NH(CH_2)_4NEt_2$		6-Cl		263P
$NH(CH_2)_4NEt_2$	OMe	6-Cl	20	134P,179P,220, 222,237
$NH(CH_2)_4NEt_2$	OMe	6-F	0.*	247
$NH(CH_2)_4NEt_2$	OMe	7-OMe		279P
$NH(CH_2)_4NEt_2$	OEt	6-Cl	7.5, 11.2	222,237
$NH(CH_2)_4NEt_2$	SMe	6-Cl	*	273P
$NH(CH_2)_4NEt_2$	OMe	$6-SO_2NH_2$		22
$NH(CH_2)_4NEt_2$	OMe	$7-SO_2NH_2$		22
$NHCH(Me)(CH_2)_3NEt_2$	I			274P
$NHCH(Me)(CH_2)_3NEt_2$		6-Cl		263P
$NHCH(Me)(CH_2)_3NEt_2$	OMe	6-Cl	6.6	222,237,263P
$NHCH(Me)(CH_2)_3NEt_2$	OH	6-Me		275P
$NHCH(Me)(CH_2)_3NEt_2$	OMe	6-Me		275P
$NHCH(Me)(CH_2)_3NEt_2$	OEt	6-Me		275P

Table 22

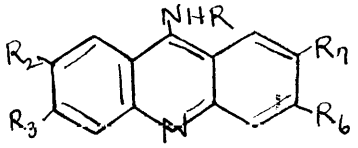
9-(δ-Diethylamino-α-methylbutyl)-aminoacridine Derivatives



R_2	R_3	Other Groups	Activity	References
Cl				263P, 274P
Br				274P
I				274P
OMe			0, +	69
	Cl			263P
	Me			263P
Cl	Cl			51P, 185
Me	OMe			263P
OH	Cl		?	238
OMe	Cl (Atabrine)		15,30	40,91,134P 179P, 206, 237,239,263P 265
OMe	Br		7.5	263P
OMe	I		+	263P
OMe	Me		+	263P
OMe	CN		23.3	245
OMe	OMe			275P
OMe	SO_2NH_2		+	22
SMe	Cl			245,273P
SEt	Cl			273P
S-iso-C_3H_7	Cl			273P
OMe		7-Cl	?	110
OMe		7-NO_2	4	237
OMe		7-SO_2NEt_2		22
OMe	Cl	4-Me	0	247
OMe	Cl	4-NO_2	weak	215
OMe	Cl	4-NH_2	0	215
OMe	Cl	7-Cl	6, +	110
OMe	Cl	7-NO_2	3.3, 6.6	238
OMe		7-OCH(Me)$_2$		275P,279P
OMe		7-OMe		279P
		3-Cl		179P
OMe	Cl	3-OMe	0	222,237
OMe	Cl	4-NH$(CH_2)_3NEt_2$	0	215
OEt	Cl		+	237
OEt	CN			247

Table AO

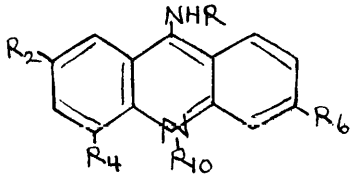
Higher 9-Dialkylaminoalkylaminoacridine Derivatives



R	Other Groups	Activity	References
$CH(Me)(CH_2)_3NMe_2$	2-OMe, 7-OMe	?	272,275P
$(CH_2)_3NEt_2$	2-OMe, 6-Cl	6	272,237,263P
$(CH_2)_3NEt_2$	2-SMe, 6-Cl	+	273P
$(CH_2)_3NEt_2$	2-Cl		274P
$(CH_2)_3NEt_2$	3-Cl		194P
$CH_2C(Me)_2CH_2NEt_2$	2-SMe, 6-Me		273P
$CH_2C(Me)_2CH_2NEt_2$	2-Me, 7-Me		275P,279P
$(CH_2)_3NEt_2$	2-OMe, 6-Cl	5	237

Table 41

Acridinium Compounds



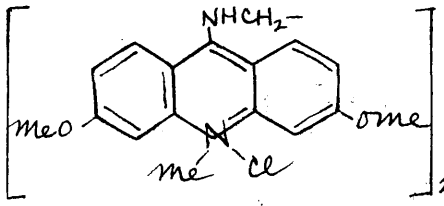
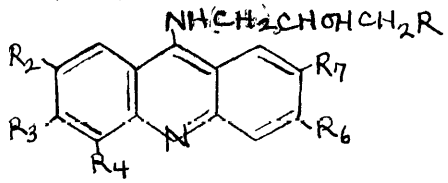
R	R_{10}	Other Groups	References
$(CH_2)_2NEt_2$	MeCl	2-OMe, 6-Cl	266P
$(CH_2)_2NEt_2$	Me_2SO_4	2-Cl	267P
$(CH_2)_2NHEt$	EtCl	2-OMe, 6-Cl	266P
$(CH_2)_4NEt_2$	C_6H_5Cl	6-Cl	266P
$CH(Me)(CH_2)_2NEt_2$	MeCl		266P
$CH(Me)(CH_2)_2NEt_2$	MeCl	2-OMe, 6-Cl	266P
$CH_2CHOHCH_2NEt_2$	MeCl	2-OMe, 6-Cl	171P, 266P
$(CH_2)_2S(CH_2)_2NEt_2$	MeOH	4-NO_2	171P
$(CH_2)_2NHCH_2CHOHCH_2NEt_2$	MeCl	2-OMe	171P
			143P
	HSO_4	3-NH_2, 6-NH_2	136

Table 42

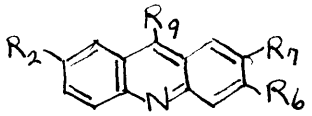
9-(γ-Amino-β-hydroxypropyl)-aminoacridine Derivatives



R	R_3	Other Groups	Activity	References
NMe_2	OMe	6-Cl		165P
NMe_2		9-NO_2		190P
NMe_2	Cl			274P
NEt_2	NMe_2		0	69
NEt_2	OMe	6-Cl	5.7	69,237,263P
NEt_2	Cl	6-NO_2		190P
NEt_2	OMe	6-NO_2		165P
NEt_2	OMe	6-CN		237
NEt_2	OEt	6-CN		237
NEt_2	NMe_2	6-Cl	Strong	69
NEt_2	OMe	7-NO_2	4	237,274P
NEt_2		1-OMe, 4-Me, 6-NO_2		190P
NEt_2	OMe	1-OMe, 4-Me, 6-NO_2		190P
NEt_2	OMe	7-OMe		275P,279P
NEt_2	OMe	7-OC_6H_{11}		275P,279P
NEt_2	SO_2NEt_2	7-OMe		172P
NEt_2	OMe	9-OMe, 6-NO_2		194P,179P
NEt_2	OMe	6-Me		194P,179P
Piperidyl	NMe_2		0	69
Piperidyl	OEt			352P,356P,358P

Table 43

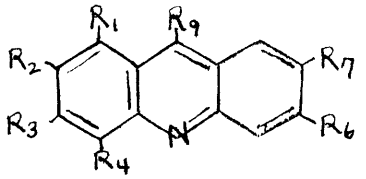
Heterocyclic Derivatives of 9-Aminoacridine



R_9	R_2	R_7	R_6	References
Morpholinyl	OMe	Cl		295
Piperidyl				179P
Piperidyl	OEt			180P
NH-4'-(1'-C_5H_9-2',3'-$(Me)_2$-5'-pyrazolonyl)	Cl	Cl		21
	Me	Cl		
	OMe	Cl		
	OMe		NO_2	
NH-2'-(4'-C_6H_6-thiazyl)	Cl	Cl		21
	Me	Cl		
	OMe	Cl		
	OMe		NO_2	
NH-2'-(4'-Me-5'-$(CH_2)_2$OH-thiazyl)	Cl	Cl		21
	Me	Cl		
	OMe	Cl		
	OMe		NO_2	
NH-6'-(2'-NH_2-benzothiazyl)	Me			90
	OMe			
	OMe	Cl		
NH-lupinyl (active)	OMe	Cl		214

Table 44

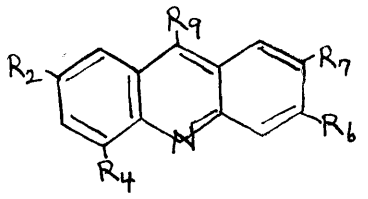
Other 9-Aminoacridine Derivatives



R_9	R_3	R_6	Other Groups	Activity	References
$NHMe$			1-NO_2, 4-OMe	0	69
NHC_6H_5	OEt				179P
$NH(CH_2)_2OH$	OEt	NH_2			109P
$NHCH_2CO_2H$	OEt	NO_2			174P
$NHCO_2Et$					109P
$NHCH(CH_2NEt_2)_2$	OMe	Cl			?63P
$NHCHOH(CH_2)_2$-piperidyl	NO_2		7-OMe	0	69
$NH(CH_2)_2O(CH_2)_2NEt_2$	SMe	Cl			?73P
$NH(CH_2)_2O(CH_2)_2NMe_2$	OMe		7-OMe		?75P
$NH(CH_2)_2S(CH_2)_2NEt_2$	SMe	Cl			?73P
$NH(CH_2)_2S(CH_2)_2NEt_2$	OMe		7-OMe		?75P
$NH(CH_2)_2N(Et)(CH_2)_2NEt_2$	OMe	Cl			?63P
$NHCH_2CHOHCH_2N(Et)CH_2$-$CHOHCH_2NEt_2$	I				?74P
$NHCH_2CONH(CH_2)_2NEt_2$	OEt	NO_2		166P,174P	190P
$NHCH_2CON(Me)(CH_2)_2NEt_2$	OEt	NO_2			166P,174P
$NHCH_2CONHCH_2CHOHCH_2NEt_2$	OEt	NO_2			166P,174P
NHC_6H_4-p-CH_2NH_2	OMe	Cl			?63P
NHC_6H_4-p-CH_2NH_2	Cl				?74P
NHC_6H_4-p-CH_2NH_2	OMe		7-SMe		?75P
NHC_6H_4-p-$O(CH_2)_2NEt_2$	OMe	Cl		+	?63P
NHC_6H_4-p-$O(CH_2)_2NEt_2$	OEt	NO_2	3-NO_2		190P
NHC_6H_4-p-$O(CH_2)_2NEt_2$	OMe		7-OMe		?75P
NHC_6H_4-p-$S(CH_2)_2NEt_2$	OMe	Cl			?73P
NHC_6H_4-p-$NH(CH_2)_2NEt_2$	OEt	NO_2			190P
NHC_6H_4-p-$N(Et)(CH_2)_2NEt_2$	OMe	Cl			?63P
NHC_6H_4-p-$NHCH_2CHOHCH_2NEt_2$	OEt	NO_2			190P
NHC_6H_4-p-$NHCH_2CHOHCH_2$-$NHCH_2NEt_2$	OEt	NO_2		100	190P
NHC_6H_4-p-CN	OEt				185P
NHC_6H_4-p-$O(CH_2)_2OH$	SMe	Cl			?73P
$NH(CH_2)_2C_6H_4$-p-OH	OEt				180P

Table A5

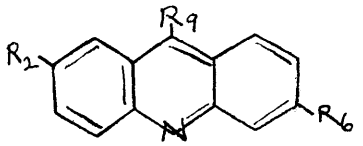
Remaining 9-Substituted Acridine Derivatives



R_9	R_2	Other Groups	Activity	References
C_6H_5	OMe	4-NH_2, 5-NH_2		326
Cl; Br; I	OMe	6-Cl		262P
OC_6H_5	OMe	6-Cl		263P
CH_2NH_2				282
$(CH_2)_2NMe_2$				282
$(CH_2)_2$-piperidyl				282
C_6H_4-p-NMe_2	Me	7-NO_2		89
$CO_2CH(Me)(CH_2)_2NEt_2$	Me	7-NO_2	0	340

Table 46

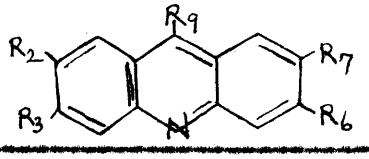
2-Substituted Acridine Derivatives



R_2	R_6	R_9	References
$NH(CH_2)_2NEt_2$			134P
$O(CH_2)_2NEt_2$	NO_2	NH_2	190P, 191P
$O(CH_2)_2$-piperidyl	NH_2	NH_2	191P
$O(CH_2)_2NEt_2$	NO_2	NH_2	191P

Table 47

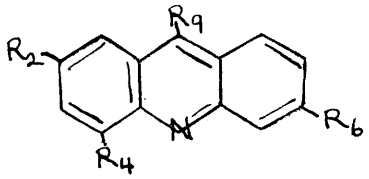
3-Substituted Acridine Derivatives



R_2	R_3	R_6	R_7	R_9	References
$O(CH_2)_2NEt_2$	$O(CH_2)_2NEt_2$	OMe	OMe		271P
$O(CH_2)_2NEt_2$	$O(CH_2)_2NEt_2$	Me	Me	Me	271P
$OCH(Me)(CH_2)_2NMe_2$	$OCH(Me)(CH_2)_2NMe_2$	Me	Me		271P
$NH(CH_2)_2NEt_2$	$O(CH_2)_2NEt_2$				271P, 352P, 356P, 358P
$NH(CH_2)_2NEt_2$	$NH(CH_2)_2NEt_2$				359P
$NHCH_2CHOHCH_2NEt_2$	$NHCH_2CHOHCH_2NEt_2$				134P

Table A8

4-Substituted Acridine Derivatives



R_4	R_2	R_6	R_9	References
$NH(CH_2)_2NEt_2$				352P, 356P, 358P
$NH(CH_2)_2$-piperidyl				357P
$NHCH_2C_6H_4$-p-NH_2				72
C_6H_4-p-$N(Et)(CH_2)_2NEt_2$	OMe	Cl	NH_2	363P
C_6H_4-p-$O(CH_2)_2NEt_2$	OMe	Cl	NH_2	363P
$O(CH_2)_2NEt_2$		NO_2	NH_2	191P

Table A9

Dihydroacridine Derivatives

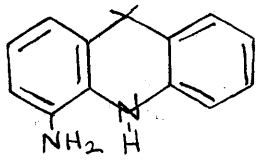
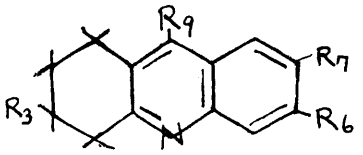
Structure	Reference
	311P

Table 50

1,2,3,4-Tetrahydroacridine Derivatives



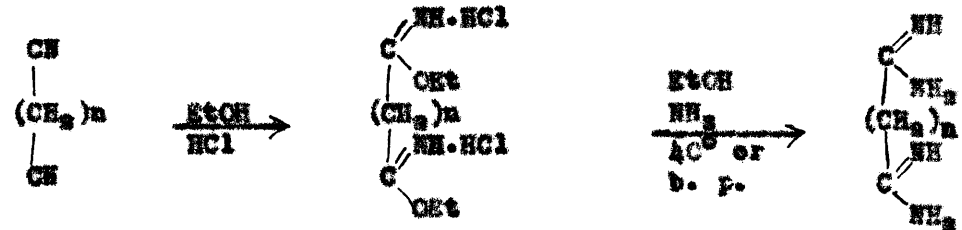
R_9	Other Groups	Activity	References
$NH(CH_2)_3NEt_2$	3-Me, 7-OMe		20
$NH(CH_2)_4NEt_2$	3-Me, 7-OMe		20
$NHCH(Me)(CH_2)_3NEt_2$	6-Cl	0	246
$NHCH(Me)(CH_2)_3NEt_2$	6-NO_2	0	246
	4-CH_2-piperidyl		198

Amidines and Guanidines

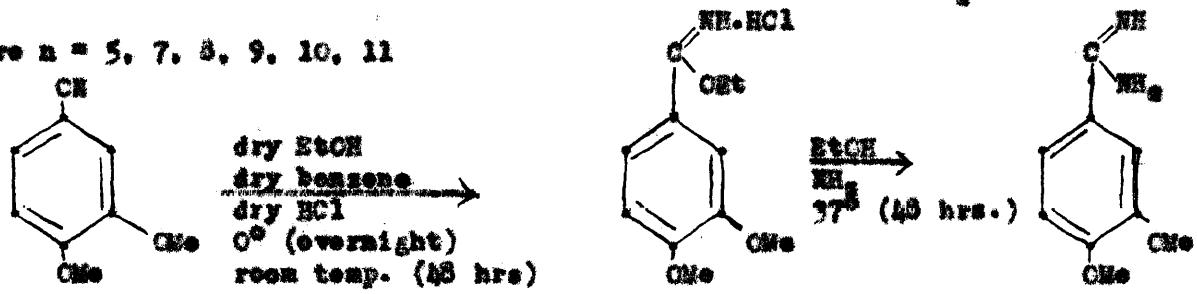
Many amidines, guanidines, and related compounds, such as isothioureas, have been prepared and tested in trypanosomal infections, but only a few have been tested in malaria. These compounds have usually been found to be inactive against P. relictum infections of canaries, but a few are active in simian and human malarial infections. Thus, 1, 11-diamidinoundecane shows no retarding action against P. relictum in canaries, but exhibits therapeutic action against P. knowlesi in monkeys, and P. vivax in man.

Amidines may be prepared by treating a nitrile with alcoholic HCl, to form the intermediate iminoether salt, followed by treatment with alcoholic ammonia to form the amidine.

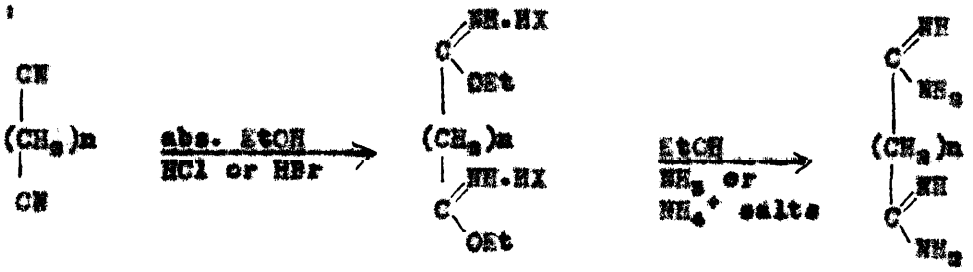
(96):



where n = 5, 7, 8, 9, 10, 11

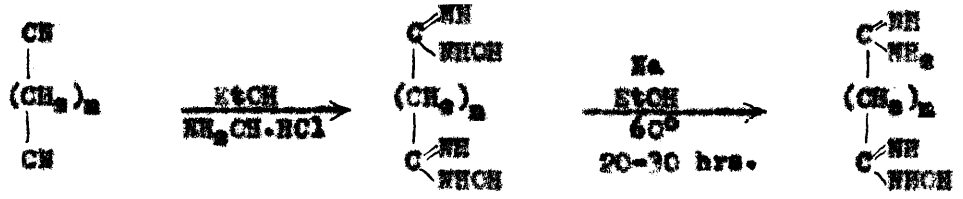


(104P):



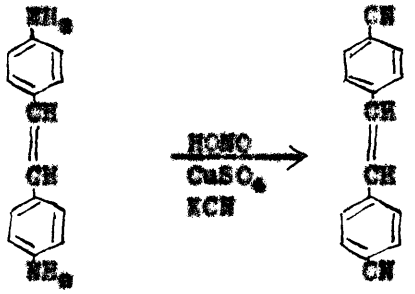
Another method is treatment of the nitrile with hydroxylamine to form the hydroxamic amide, which is not isolated, followed by reduction to the amidine.

(225):

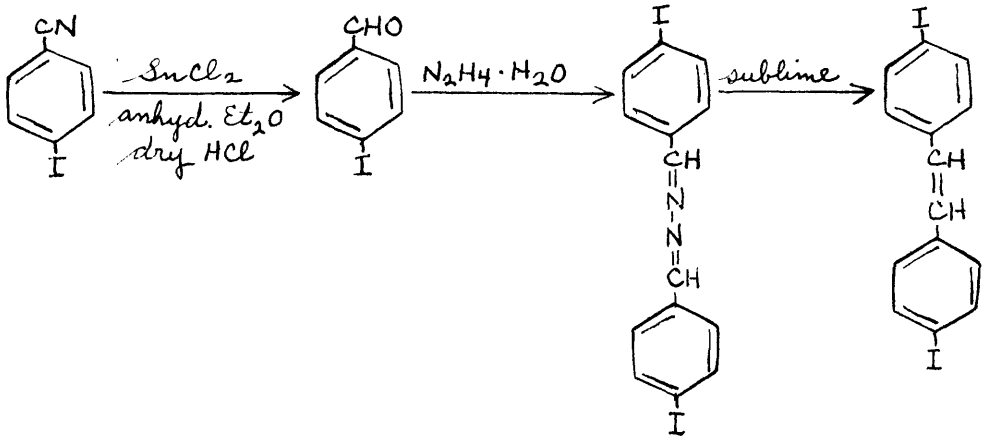


4,4'-Diamidinostilbene has been prepared from 4,4'-dicyanostilbene by the usual procedure (1C&P) and by an interesting series of reactions by Sah (930). The 4,4'-dicyanostilbene is prepared from 4,4'-diaminostilbene through the di-diazonium salt.

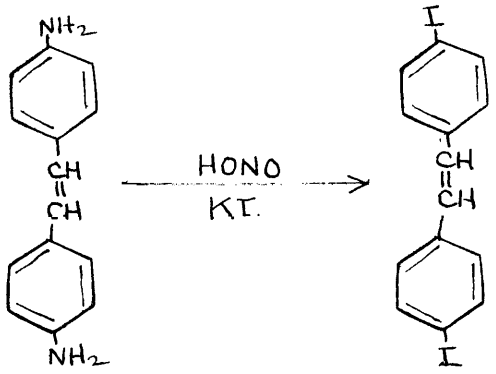
(225):



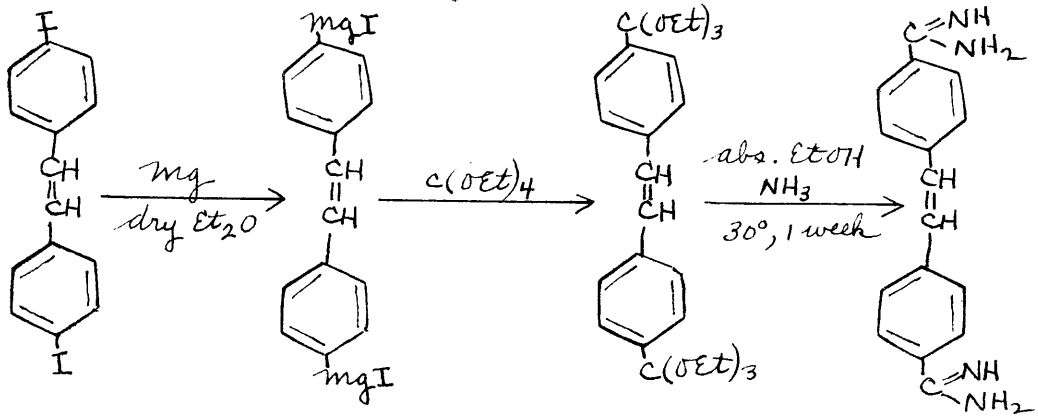
Sah prepared his intermediate compound, 4,4'-diiodostilbene, in two ways. Stephen reduction of 4-iodobenzonitrile produced 4-iodobenzaldehyde which was reacted with hydrazine hydrate to form the azine. Pyrolysis of the azine produced the desired stilbene derivative.



The second method was substitution of amino groups with iodine in 4,4'-diaminostilbene through the di-diazonium salt.

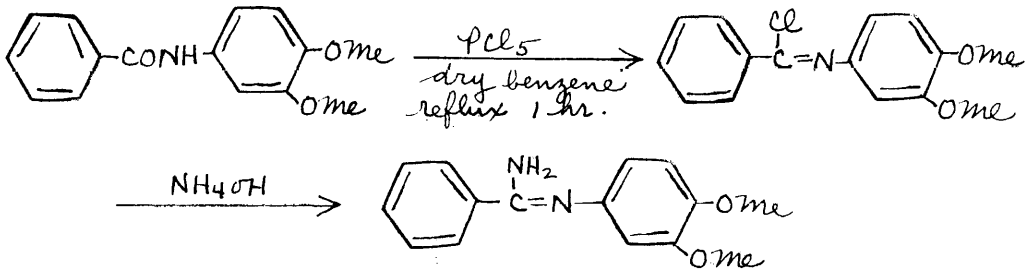


The 4,4'-diiodostilbene was converted into the di-Grignard compound which was treated with ethyl orthocarbonate to form the di-orthoester. This was converted into silbamidine by treatment with alcoholic ammonia.



Barber and Slack (16) prepared 4,4'-dicyanostilbene from 4,4', α, β -tetrabromodiphenylethane.

N-substituted amidines can be prepared from N-substituted amides. The preparation of N-veratrylbenzamidine is of this type. (54):



p-Carboxyphenylguanidine has been prepared by the following series of reactions:

(96)

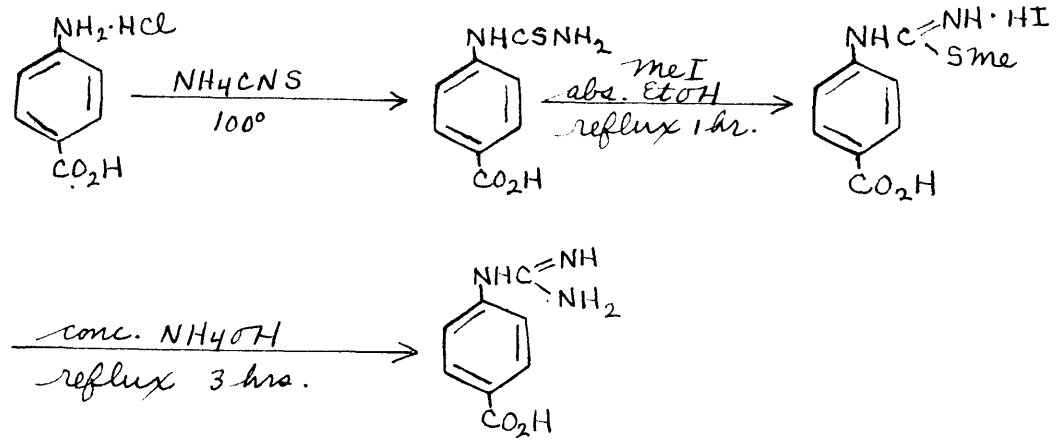
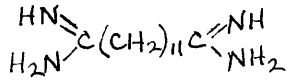
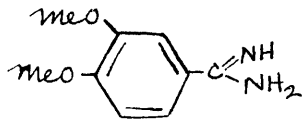
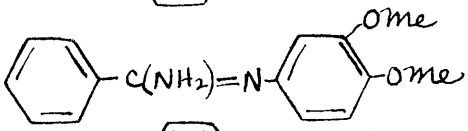
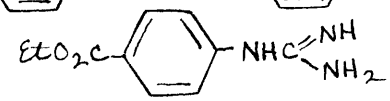
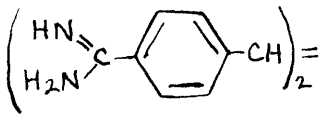
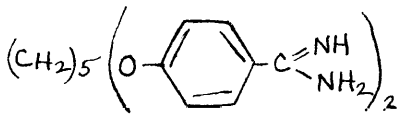


Table 51

Amidines and Guanidines

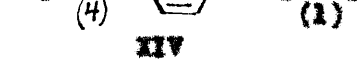
Structure	Parasite	Host	Activity	References
	P. vivax	Man	+	193
	P. knowlesi	Monkey	+	70
	P. relictum	Canary	0	70
		Canary	0	96
		Canary	0	96
		Canary	0	96
	P. knowlesi	Monkey	+	122,401
	P. vivax	Man	+	401
	P. falciparum	Man	0	401
	P. relictum	Canary	0	122
	P. knowlesi	Monkey	+	122,401
	P. relictum	Canary	+	122,401

Sulfonamides and Sulfones

It was shown by Coggeshall (75,76) that sulfanilamide completely cures P. knowlesi infections in rhesus monkeys. However, this compound has only a slight action on the course of human malaria. Other sulfonamides are definitely active both in simian and in human malaria (68, 69, 77, 966), but these drugs were found by several investigators to be without effect in avian malaria. Thus, sulfanilamide and sulfapyridine were found (53,76,253) to have no effect on P. relictum, P. cathemerium, and P. nucleophilum infections of canaries; sulfanilamide derivatives having aminoalkylamino sidechains were inactive in P. relictum infections (283); several sulfonamides were found to have no effect on P. lophurae infections of ducks and chickens (76,147). Opposed to these results are the observations that prontosil soluble caused complete disappearance of parasites in P. praecox infections in Java sparrows (?), and that sulfapyridine is effective against P. circumflexum infections in canaries (253).

An explanation has been offered (256) that the discrepancy between the responses of simian and human malaria and the response of avian malaria to treatment with sulfonamides may be due to a difference in species susceptibility of parasites, but perhaps also the discrepancy is due only to dissimilar blood concentration-time relationships due to host differences in absorption and excretion.

The sulfanilamide nucleus is numbered in this paper according to the system of Crossley, Northey and Hultquist (82), as shown in formula XIV. Thus, this compound would be named N^4-acetyl-N^1-dimethylsulfanilamide.



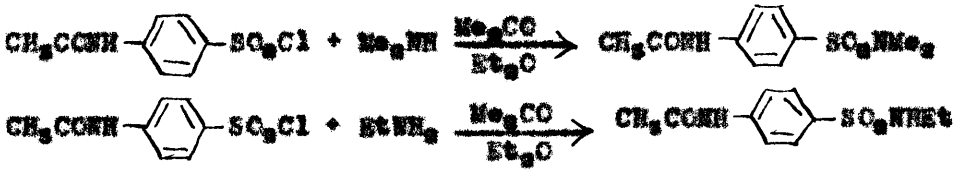
XIV

The synthesis of N^1-substituted sulfanilamides generally utilizes N-acetyl sulfanilyl chloride, which is prepared from acetanilide and chlorosulfonic acid.

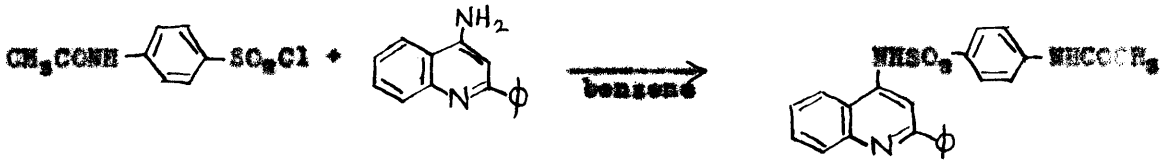
(297):

The acetyl sulfanilyl chloride is reacted in acetone-ether or benzene solution with an amine or imine to form the N^1-substituted N^4-acetyl sulfanilamide.

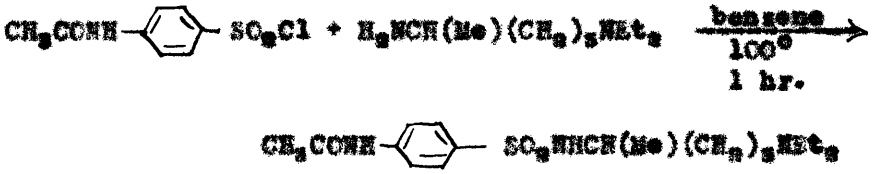
(391):



(23):

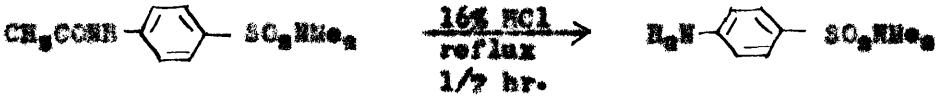


(93):



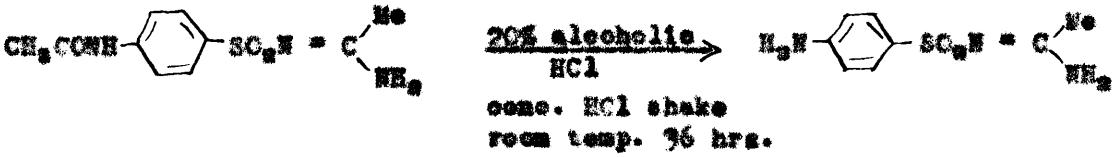
The N^4-acetyl group is hydrolyzed off by boiling with aqueous or alcoholic hydrochloric acid.

(391):



(23):

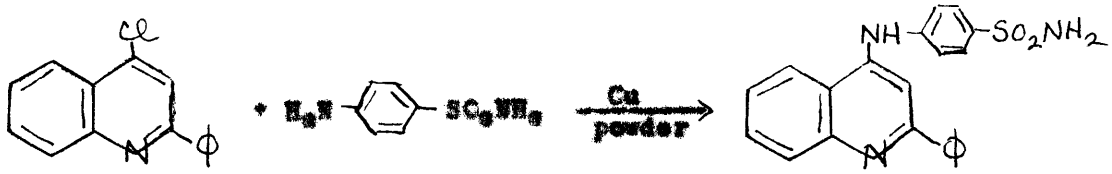
(224):



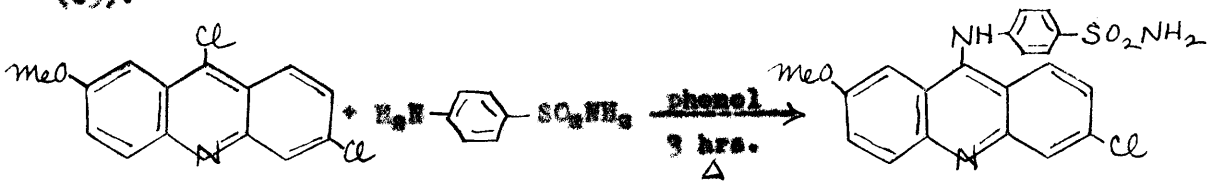
N^4-Substituted sulfanilamides may be prepared from sulfanilamide by reaction with an alkyl or aryl halide, or with an acyl halide. The N^1-amino group is untouched in this process.

(93):

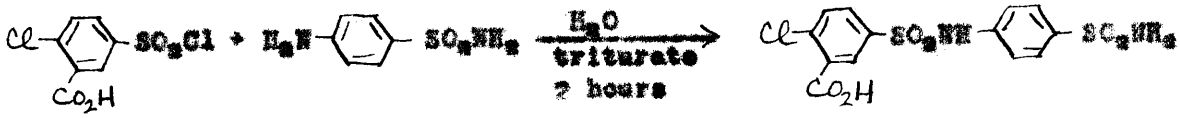
(73):



(69):

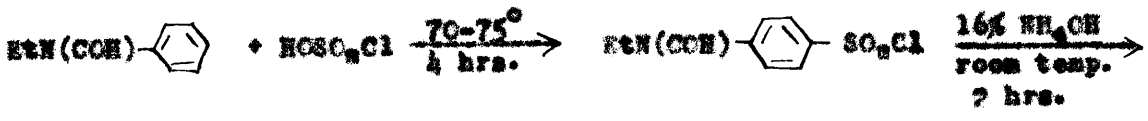


(84):



N^4-Substituted sulfanilamides may be prepared by reacting suitable N-substituted anilines with chlorosulfonic acid followed by treatment with ammonium hydroxide.

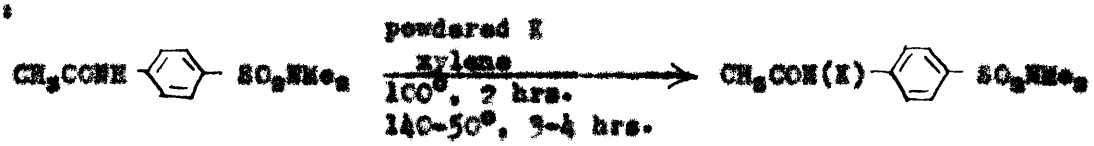
(391):



The synthesis of N^1,N^4-substituted sulfanilamides involves the reaction of an alkyl, aryl, or acyl halide with an N^1-substituted

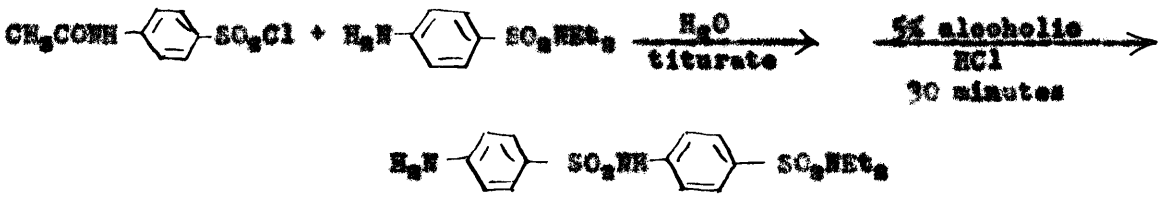
sulfanilamide or with an N^4-acyl-N^1-substituted sulfanilamide.

(391):



(84):

(84):



(93):

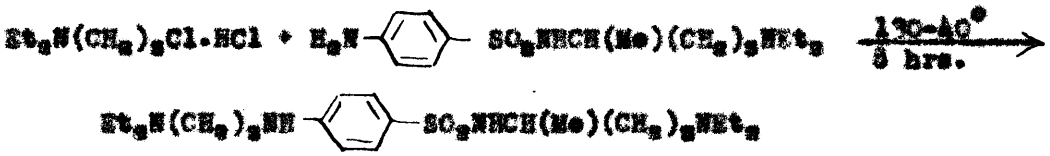
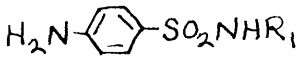


Table 52

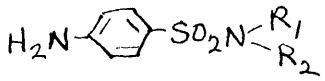
N^1-Substituted Sulfanilamides



R_1	Activity	References
H (sulfanilamide)	O Avian O Human + Monkey	76,77,106,227,253
NH_2		256
CH	+	256
Me	+	256
$C(=NH)NH_2$	+	256
$C(=NH)NHMe$	+	256
$CH_2CHCHMe$	±	256
$CH(Me)(CH_2)_2NEt_2$		89
$CH_2CHOHCH_2NEt_2$		89
C_6H_4-p-CH	O	89,255
C_6H_4-3-SO_2H	O	256
C_6H_4-p-SO_2H	+	25P
SO_2NH-C_6H_4-p-$SO_2NHC_6H_4$-p-SO_2H	O	256
C_6H_3-3,5-$(Cl)_2$	+	25P
C_6H_3-3,5-$(Br)_2$	+	25P
C_6H_3-3,5-$(CF_3)_2$	++	25P
C_6H_2-3,4,5-$(Cl)_3$	+	25P
2'-Pyridyl (Sulfapyridine)	+,O	77,253
4'-(2'-C_9H_6N-6'-OMe-quinolyl)		23
2'-Pyrimidyl (Sulfadiazine)	+	256
2'-(4'-Me-pyrimidyl)	+	256
2'-Pyrazyl	+	256
2'-Thiazyl (Sulfathiazole)	+	77,393
8'-(6'-MeO-quinolyl)		105P
C_6H_4-p-SO_2NMe_2 (Uleron)	+	256

Table 53

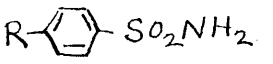
N^1,N^1-Substituted Sulfanilamides



R_1	R_2	Activity	References
Me	Me	+	256
$(CH_2)_5CH$	$(CH_2)_5CH$	0	256
Me	2'-Thiazyl		256
C_6H_5	$(CH_2)_5CH$		256
$-(CH_2)_5-C-(CH_2)_5-$			256

Table 54

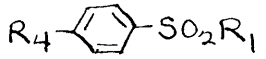
4-Substituted Benzenesulfonamides



R	Activity	References
NC_5	0	256
$NH(CH_2)_2NEt_2$		93
$NHCH_2C_6H_5$ (Proseptasine)	+,0	367
4'-(2'-C_9H_6N-quinolyl)		23
9'-(2'-OMe-6'-Cl-acridyl)		69
$NHSO_2C_6H_4$-p-NH_2 (Disulon)	+	256
$NHSO_2C_6H_4$-m-NH_2	0	256
$NHSO_2$-2'-[7'-OMe-9'-NHCH(Me)$(CH_2)_3NEt_2$-acridyl]		84,87
N=NC_6H_3-m,p-$(NH_2)_2$		257
N=NC_6H_3-o,p-$(NH_2)_2$ (Prontosil)		67,106,387
N=N-4'-(6'-OH-quinolyl)	0	283

Table 55

N^1-N^4-Substituted Sulfanilamides



R_1	R_4	Activity	References
$NH(CH_2)_2NEt_2$	NMe_2		391
$NH(CH_2)_2NEt_2$	NEt_2		391
$NH(CH_2)_2NEt_2$	Piperidyl		391
$NHCH(Me)(CH_2)_3NEt_2$	$NH(CH_2)_3NEt_2$		93
NHC_6H_3-3′,5′-$(Cl)_2$	NMe_2	+	25P
"	Piperidyl	+	25P
"	NHCOEt	+	25P
"	$NHCOCH_2C_6H_5$	+	25P
"	$N{=}CHC_6H_4$-2-OH		25P
"	$N{=}CHC_6H_4$-4-OMe	+	25P
NHC_6H_3-3′,5′-$(Br)_2$	$N{=}NC_6H_5$	+	25P
"	NHCOMe	+	25P
"	$N{=}CHCH{=}CHC_6H_4$-4-NH_2	+	25P
"	$NHNHC_6H_5$	+	25P
NH-8′-(6′-MeO-quinolyl)	$NHCH_2C_6H_5$		105P
NHC_6H_4-p-CO_2NEt_2	NH-9′-(2′-MeO-6′-Cl-acridyl)		87
NEt_2	$N{=}R$-5′-(6′-OH-7′-$NHMe$-quinolyl)		283
NEt_2	NH-2′-7′-MeO-9′-NHCH-(Me)$(CH_2)_3NEt_2$-acridyl		87

Table 56

Isomeric Sulfanilamides

Compound	Activity	References
$H_2NC_6H_4$-2'-SO_2NH_2	0	256
$H_2NC_6H_4$-3'-SO_2NH_2	0	256
$H_2NC_6H_4$-3'-$SO_2NHC_6H_4$-2*-CO_2H	0	256
$H_2NC_6H_4$-3'-$NHSO_2NHC_6H_4$-3*-$SO_2NHCH_2CH_2OH$	0	256

Table 57

Acridine Sulfonamides

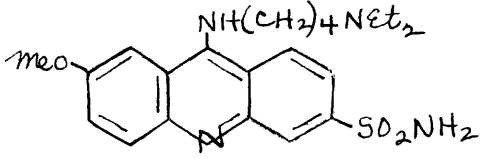
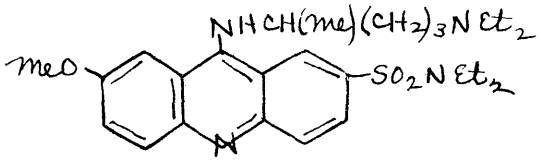
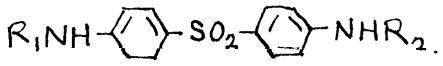
Structure	References
	22
	22

Table 58

Sulfones



R_1	R_2	Activity	References
H	H	0	256
Glucose sulfonate	Glucose sulfonate	+	77
EtCO	EtCO		256
MeCO	MeCO	±	256
H	MeCO	+	256

Remaining Antimalarials

The compounds listed in the following tables are representative of those compounds which are not derivatives of quinoline and acridine and which are not amidines, sulfonamides, or sulfones, which have been prepared or tested as antimalarials. Most of these compounds have not been tested for antimalarial activity, and of those which have been tested only a very few have exhibited even slight activity.

Table 52

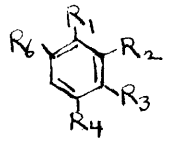
a. Aliphatic Compounds

Structure	Activity	References
$CH_3CHNH_2CO_2H$	0	377
$CH_3(CH_2)_{10}CO_2(CH_2)_2NMe_2{}^+CH^-$	0	115
$CH_3CH(NH_2)(CH_2)_3NEt_2$	0, slight	122
$(iso\text{-}C_5H_{11}NH)_2(CH_2)_{10}$	0	400
$[(C_5H_{11})_2N]_2(CH_2)_{10}$	0	122
$NH_2CH_2CHOHCH_2NEt_2$		186P
$(Et_2NCH_2CHOH)_2(CH_2)_8$	0	400
$[Et_2N(CH_2)_3NH]_2(CH_2)_{10}$	0	400
$[(Me)(Et)N(CH_2)_2NH]_2CO$		342P
[Piperidyl-$CH_2C(OH)(C_3H_7)$]$_2(CH_2)_{10}$	0	931

Table 60

b. Aromatic Compounds

1. Benzene Derivatives



R_1	Other Groups	Activity	References
OH	4-NO	O	146
OH	3-OH, 4-NO	O	146
OH	3-OH, 4-n-C_6H_9	O	146
OH	3-OH, 4-n-C_8H_{17}	O	146
OH	2-NO_2, 4-NO_2, 6-NO_2	O	146
N=NC$_6$H$_5$	2-OH, 3-OH, 4-OH	O	146
N=NC$_6$H$_5$	2-NH_2, 4-NH_2	O	146
N=NC$_6$H$_4$-p-NHCH(Me)(CH$_2$)$_3$NEt$_2$	4-OMe		17CP
N=NC$_6$H$_3$-o-Cl-p-NHCH(Me)(CH$_2$)$_3$NEt$_2$	4-OMe		17CP
CO_2H	4-NH_2		256
$CH_2CHCHCH_2NMe_2$	2-OMe, 4-OMe	O	115
$CH_2CHCHCH_2$-piperidyl	3-Me	O	115
$CH_2NHCH_2CHCHCH_2CO_2H$	4-OEt	10-senary, O-man	115
$CH_2NHCH_2CHOHCH_2NHCH_2C_6H_5$		O	115
N(Me)(CH$_2$)$_3$NEt$_2$	4-OH		158P
N(Me)(CH$_2$)$_3$NEt$_2$	4-NH(CH$_2$)$_3$NEt$_2$		61P
NHCH(Me)(CH$_2$)$_3$NEt$_2$		O	165P, 339P
N(Et)CH(Me)(CH$_2$)$_3$NEt$_2$	3-OH		158P
NH(CH$_2$)$_2$S(CH$_2$)$_2$NEt$_2$	3-OMe, 4-OC_3H_7-iso		6CP
$NHCH_2CHCHCH_2NMe_2$	2-Me	O	115
$NHCH_2CHCHCH_2NMe_2$	3-Me	O	115
$NHCH_2CHCHCH_2NMe_2$	4-Me	+-senary, O-man	115
N=C(Me)CHCH$_2$CH$_2$ (CO—O)	4-OMe		7P
N=C(Me)CHCH$_2$CH$_2$ (CO—O)	4-$CO_2CH(Me)CH(Me)NMe_2$		7P
OC_6H_5	4-NH(CH$_2$)$_3$NEt$_2$		169P
OC_6H_3-o-OMe-p-$CH_2CH=CH_2$	4-N[(CH$_2$)$_3$NEt$_2$]$_2$		169P
OC_6H_4-m-OMe	2-N[CH(Me)(CH$_2$)$_3$NEt$_2$]$_2$ 4-N[CH(Me)(CH$_2$)$_3$NEt$_2$]$_2$		169P
SC_6H_4-p-OMe	4-NHCH(Me)(CH$_2$)$_3$NEt$_2$		169P
SC_6H_4-p-N[(CH$_2$)$_3$NEt$_2$]$_2$	4-N[(CH$_2$)$_3$NEt$_2$]$_2$		169P

Table 61

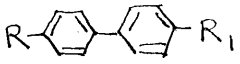
b. 2. Aromatic Substituted Ureas

$RNHCONHR_1$

R	R_1	Activity	References
C_6H_4-p-NMe_2	H		124,342P
C_6H_4-p-NEt_2	H	+	124
C_6H_4-p-$N(C_5H_{11})_2$	H		124
C_6H_4-m-$O(CH_2)_2NEt_2$	6-Quinolyl		342P
C_6H_5-p-OC_6H_3-3,5-$(Me)_2$	6-Quinolyl		342P
C_6H_5-m-NO_2-p-NMe_2	H		124,342P

Table 62

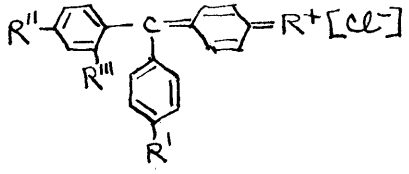
b. 3. Diphenyl Derivatives



R	R_1	Activity	References
$CHOHCH_2$-piperidyl	H		400
$NH(CH_2)_2NH_2$	H	0	400
$NH(CH_2)_3NH_2$	H	0	400
$CHOHCH_2$-piperidyl	H	0	400
$NHCH_2CHOHCH_2NMe_2$	H	0	115

Table 63

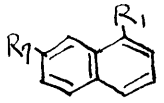
b. 4. Triphenylmethane Derivatives



R	R'	R''	R'''	References
$NMe(CH_2)_2NEt_2$	$N(Me)(CH_2)_2NEt_2$	H	Me	352P, 356P, 358P

Table 64

b. 5. Naphthalene Derivatives



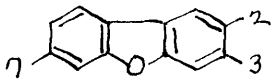
R_1	R_7	Activity	References
$CHOHCH_2$-piperidyl	OMe	0	209
$CH_3CHOHCH_2NEt_2$		slight-birds 0-mam	115
$NHCH_2CHOHCH_2NMe_2$		slight-birds 0-mam	115

Table 65

c. Heterocyclic Compounds

1. Ring Systems Containing Oxygen

a. Diphenylene Oxides



Substituents	References
3-$N\left[(CH_2)_2NEt_2\right]_2$; 7-$N\left[(CH_2)_2NEt_2\right]_2$	169P
2-$N\left[(CH_2)_2O(CH_2)_2NEt_2\right]_2$	169P

Table 66

e. 1. b. Xanthene Derivatives

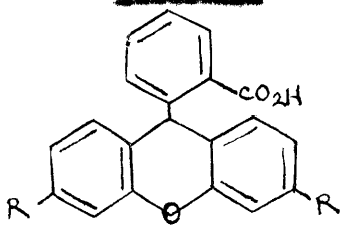
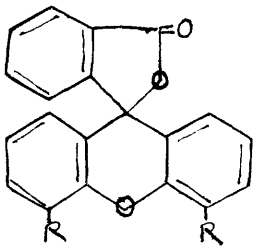
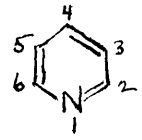
Structure	Activity	References
 R = N(Et)(CH₂)₂NEt₂	+	349P, 352P, 356P, 358P, 359P
 R = N(Me)(CH₂)₂NEt₂	+	352P, 356P, 358P

Table 67

e. 2. Ring Systems Containing One Nitrogen

a. Pyridine Derivatives



Substituents	Activity	References
2-CH, 5-NO₂	0	146
2-CMe, 5-NH₂	0	146
2-Piperidyl, 6-N[(CH₂)₂OH]₂		396P
2-O(CH₂)₂NH₂, 3-CONHC₆H₅		270P
2-O(CH₂)₂NEt₂, 3-CONHC₆H₄-p-OEt		270P
2-O(CH₂)₂-piperidyl, 3-CONHC₆H₅		270P
2-NH(CH₂)₂NEt₂		352P
2-OC₆H₅, 5-NHCH(Me)(CH₂)₂NEt₂		169P
3-NO₂, 4-NHCONH-4'-pyridyl		342P
1-(CH₂)₂N(C₆H₁₁)₂, 2=NH, 5-OEt		94P

Table 68

e. 2. b. Piperidine Derivatives

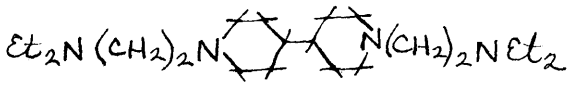
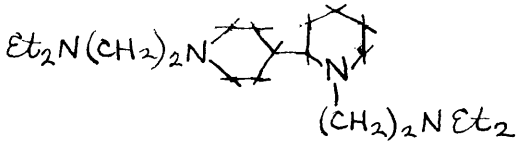
Structure	Activity	References
	0	400
	0	400

Table 69

e. 2. c. Quinuclidines

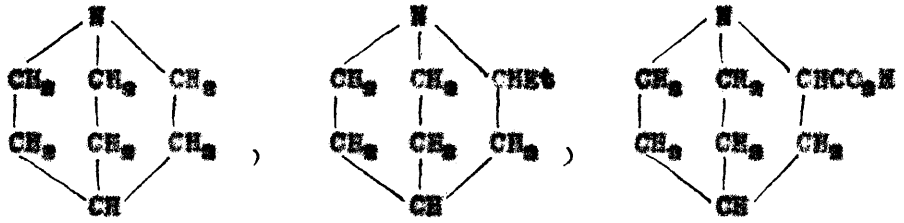
Structures	References
	196P

Table 70

e. 2. d. Carbazole Derivatives

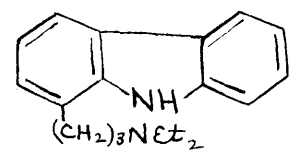
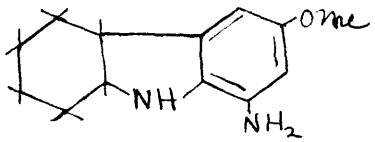
Structure	References
	27
	328

Table 71

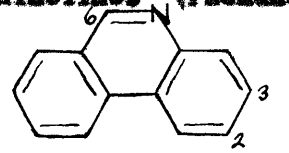
e. 2. e. Perhydrocarbazole Derivatives

R_2	R_4	References
$(CH_2)_2N(Me)CH_2C_6H_5$		35P
$(CH_2)_2$-1'-(2'=NH-pyridonyl)	CHt	35P
$(CH_2)_2NHC_6H_4$-p-O$(CH_2)_2NEt_2$		35P

Table 72

e. 2. f. Benzoquinoline Derivatives

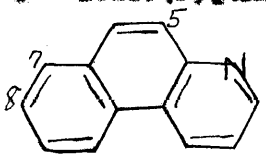
1. Benzo(c)quinolines (Phenanthridines)



Substituents	Activity	References
2-Br, 6-NH$(CH_2)_2NEt_2$	0	394
3-OMe, 6-NH$(CH_2)_2NEt_2$	0	394
6-NHCH(Me)$(CH_2)_2NEt_2$	0	394

Table 73

a. 2. f. 2. Benzo(f)quinolines



Substituents	References
5-NH$(CH_2)_3NEt_2$	18
5-NHCH(Me)$(CH_2)_3NEt_2$, 7-OMe	173P
5-NHCH(Me)$(CH_2)_3NEt_2$, 8-Br	173P

Table 74

a. 2. f. 3. Benzo(g)quinolines

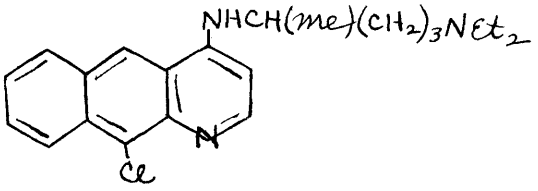
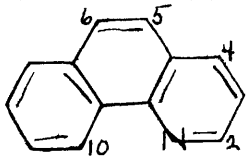
Structure	References
	173P

Table 75

e. 2. f. 4. Benzo(h)quinolines



Substituents	References
4-NH$(CH_2)_2S(CH_2)_2NEt_2$	173P
2-NH$(CH_2)_4NEt_2$. 4-Me	986
4-NHCH(Me)$(CH_2)_3NEt_2$. 5-OMe	173P
4-NHCH(Me)$(CH_2)_3NEt_2$. 6-Cl	173P
4-NHCH(Me)$(CH_2)_3NEt_2$. 10-Cl	173P

Table 76

e. 2. f. 5. Iso-quinolines

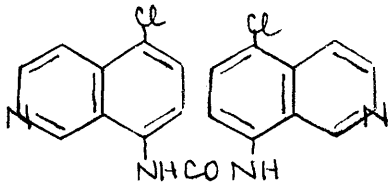
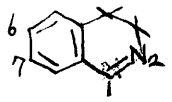
Structure	Reference
	942P

Table 77

o. ?. f. 6. Dihydroisoquinolines



Substituents	Activity	References
1-CH_2Cl, 6-OMe, 7-OMe	0	64P,66
1-$(CH_2)_4Cl$, 6-OMe, 7-OMe	0	64P,66
1,2=$(CH_2)_3$, 2-Cl, 6-OMe, 7-OMe	0	66
1-$(CH_2)_3$-1'-[6',7'-$(OMe)_2$-3',4'-dihydroisoquinolyl], 6-OMe, 7-OMe	0	65

Table 78

o. ?. f. 7. Tetrahydroisoquinolines

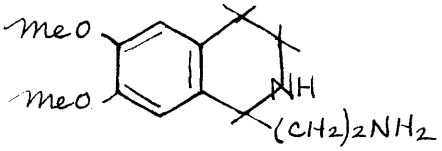
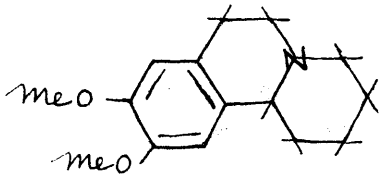
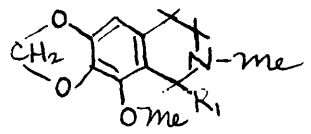
Structure	Activity	References
	0	66
	0	66

Table 79

e. 2. f. 8. Centarmine Derivatives

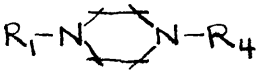


R_1	References
C_6H_3-2'-NH_2-5'-OEt	3
$CH_2C_6H_4$-p-NO_2	3
CH_2-2'-pyridyl	79
4'-[3',5'-$(Me)_2$-pyrazolyl]	3

Table 80

e. 3. Ring Systems Containing Two Nitrogens

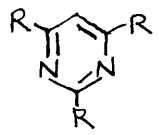
a. Piperazines



R_1	R_4	Activity	References
$CH_2CHCHCH_2C_6H_5$	R_1	0	115
$CH_2CHCHCH_2OC_6H_5$	H	0	115

Table 81

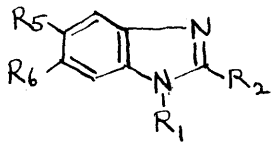
e. 3. b. Pyrimidines



R	References
OC_6H_5	231
OC_6H_4-p-Cl	231
OC_6H_4-p-OMe	231

Table 82

e. 3. e. Benzimidazoles



Substituents	Activity	References
2-$(CH_2)_2NH_2$	0	62
2-$(CH_2)_2NH_2$, 6-OEt		62
1-$(CH_2)_2NEt_2$, 2-Me, 6-OMe		294
5-NH$(CH_2)_2NEt_2$, 6-OMe		294

Table 83

e. 9. d. Carboline Derivatives and Related Compounds

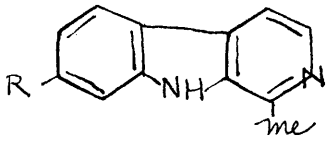
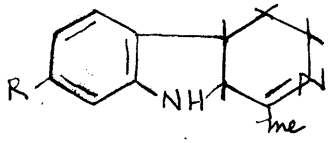
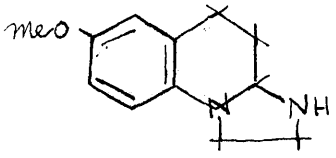
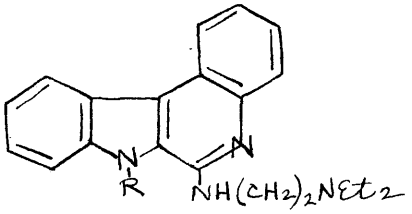
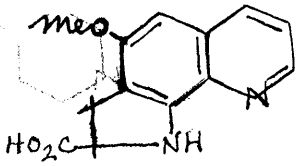
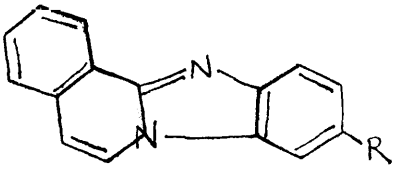
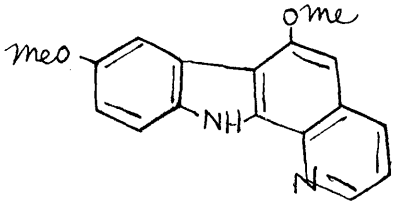
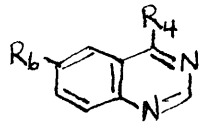
Structure	R	Activity	References
	OMe (Harmine)	0	139
	O-n-C_4H_9	0	81,315P
	O-n-C_7H_{15}	0	81
	$O(CH_2)_3NEt_2$	0	81,315P
	OMe (Harmaline)	+, 0	81,129P
	O-n-C_4H_9	+, 0	81,315P
			362
	H		202
	Me		202
			290
	H		284P
	NO_2		284P
	NH_2		284P
			164P

Table 84

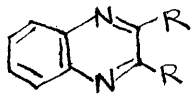
o. 3. e. Quinazolines



R_4	R_6	Activity	References
$NH(CH_2)_3NEt_2$		0	236
$NH(CH_2)_3NEt_2$	Cl	0	236
$NHCH(Me)(CH_2)_3NEt_2$	Cl	0	236
$NHCH(Me)(CH_2)_3NEt_2$	NO_2	0	236

Table 85

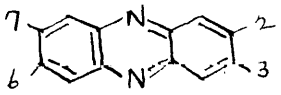
o. 3. f. Quinoxalines



R	References
OC_6H_4-p-OMe	231
NHC_6H_4-p-Me	231
C_6H_4-m-Me	231

Table 86

e. 3. g. Phenazines



Substituents	References
2-Me, 3-N(Me)$(CH_2)_2NEt_2$, 7-Me	359P, 356P, 353P
3-N(Me)$(CH_2)_2NEt_2$, 6-NH$(CH_2)_2NEt_2$, 7-Me	346P

Table 87

e. 3. h. Phenanthrolines

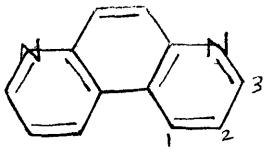
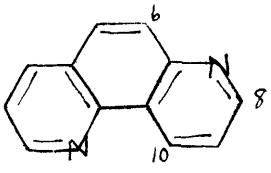
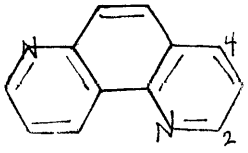
Structure	Substituents	References
	2-NH$(CH_2)_2NEt_2$	179P
	1-Me, 3-NH$(CH_2)_2NEt_2$	203
	1-Me, 3-Piperazyl	203
	1-NHCH(Me)$(CH_2)_2NEt_2$, 3-Me	179P
	8-NHCH(Me)$(CH_2)_2NEt_2$	204
	8-Me, 10-NHCH(Me)$(CH_2)_2NEt_2$	204
	6-NMe_2	37P
	6-NH$(CH_2)_2CH$	37P
	2-NHCH(Me)$(CH_2)_2NEt_2$, 4-Me	204
	2-Me, 4-NHCH(Me)$(CH_2)_2NEt_2$	204

Table 88

c. 4. Ring Systems Containing Three or More Nitrogens

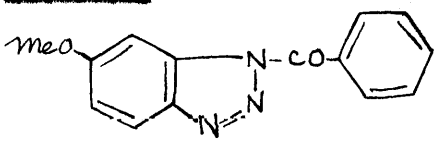
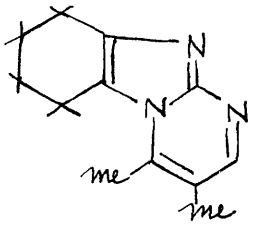
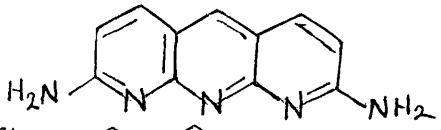
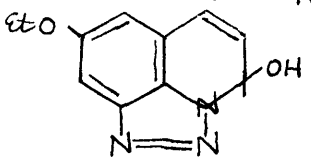
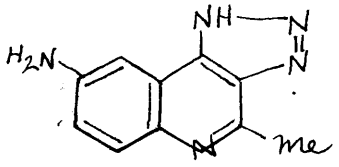
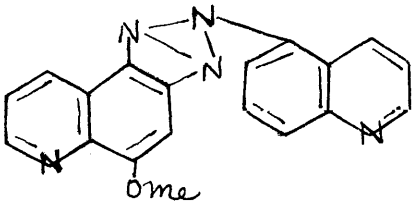
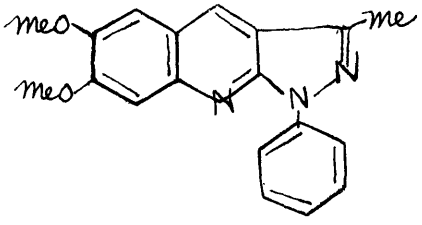
Structure	References
	182
	327P
	339P
	1P
	184P
	149P
	292

Table 89

e. 5. Ring Systems Containing Oxygen and Nitrogen

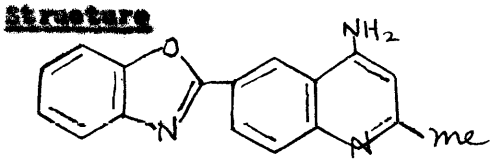
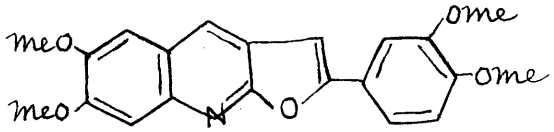
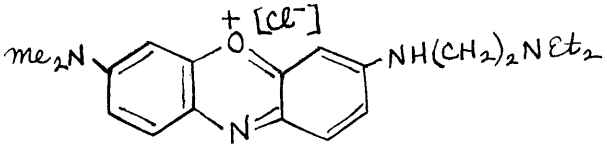
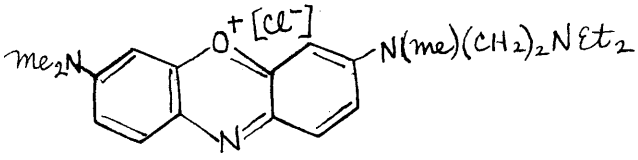
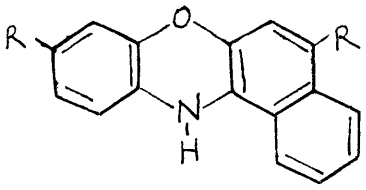
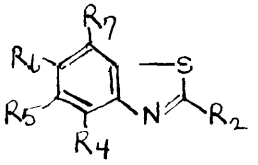
Structure	References
	176P
	142
	347P
	347P, 350P, 356P, 358P, 359P
 $R = N(Et)(CH_2)_2NEt_2$	347P

Table 20

c. 6. Ring Systems Containing Sulfur and Nitrogen

a. Benzothiazoles

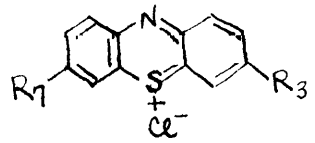


Substituents	Activity	References
2-NH$(CH_2)_3NEt_2$. 5-OMe	0	294
2-NH$(CH_2)_3NEt_2$. 6-OMe	0	294
2-$NHCH_2CHCHCH_2$-piperidyl	0	92
2-NHCH(Me)$(CH_2)_2NEt_2$	0	92
2-NHCH(Me)$(CH_2)_3NEt_2$. 6-Cl	0	92
4-NH$(CH_2)_2NEt_2$. 6-OMe		119
5-OMe. 7-NH$(CH_2)_3NEt_2$	0	219
5-OMe. 7-NH-lupinyl	0	72
2-[6'-(4'-NH$(CH_2)_3CHMe_2$-quinolyl)]. 6-OMe		176P
2-[6'-(4'-$NHCH_2CHCHCH_2NEt_2$)]. 6-Me		176P
2-(9'-$NHCH_2CHCHCH_2NEt_2$-acridyl). 6-Me		176P

Table 91

e. 6. b. Phenothiazines

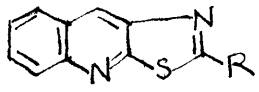
Phenazthionium Chlorides



R_1	R_3	Therapeutic Index	References
NMe_2 (Methylene Blue)	NMe_2	6. 10	112.117.295
$NH(CH_2)_3NEt_2$	NMe_2		352P.356P.358P. 359P
$N(Me)(CH_2)_3NEt_2$	NMe_2	•	272.352P.356P. 358P.359P
$NH(CH_2)_3$-piperidyl	NMe_2		352P
$N(Me)(CH_2)_3$-piperidyl			169P
$N(Me)CH(Me)CH(Me)CH_2NMe_2$	NMe_2		352P.356P.358P. 359P
$N(Me)CH_2CHOHCH_2NEt_2$	NMe_2		352P.356P.358P
$NH(CH_2)_3NEt_2$	$NH(CH_2)_3NEt_2$		352P.356P.358P
NH-4'-(2'-Me-6'-OMe-quinolyl)	R_3		151

Table 92

e. 6. e. Thiazoloquinolines



R	References
NHC_6H_4-p-OMe	125
NHC_6H_4-p-Me	125

Table 93

e. 6. d. Thiophenanthrolines

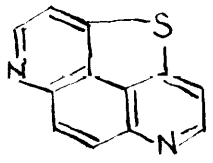
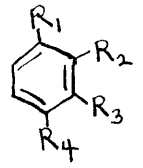
Structure	Reference
	1181

Table 24

d. Arsenic Compounds

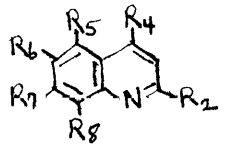
1. Benzene Derivatives



R_1	R_2	R_3	Activity	References
AsO	(3-NH_2)	OH (Mapharsen)	slight	402
AsO_3H_2		$NHCH_2CONH_2$ (Tryparsamide)		402
AsO_3H_2		$NHCH_2CO$-piperidyl		115
AsO_3HNa	NH_2	OH		115
AsO_3HNa	NHCOMe	OH (Stovarsol)	+	115,121,954
AsO_3HNa		NH_2 (Atoxyl)		121
AsO_3HNa	OH	NH_2		115
AsO_3HNa	OH	NHCOMe (Orsanine)		115
AsO_3HNa		5'-C_6H_3-2',3'-diketopyrrolidinyl		115
OH	NH_2	As=AsC_6H_3-3'-NH_2-4'-OH (Salvarsan, Arsphenamine)	+	119
ONa	NH_2	As=As(ONa)(Ag)C_6H_3-3'-NH_2-4'-ONa (Silver Arsphenamine)	+	780
OH	NH_2	As=AsC_6H_3-3'-$NHCH_2SO_2Na$-4'-OH (Neoarsphenamine, Neosalvarsan, Novarsenobillon)	0	395

Table 25

d. 2- Quinoline Derivatives

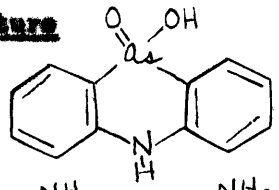
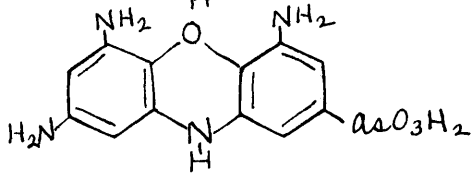
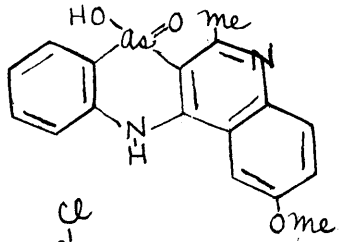
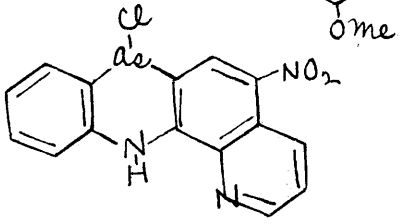
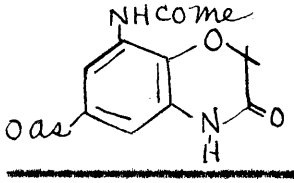


R_2	References
NHC_6H_4-2'-AsO_3H_2	372
NHC_6H_4-3'-AsO_3H_2	371
NHC_6H_4-4'-C_6H_4-4"-AsO_3H_2	371
NHC_6H_3-2'-Me-4'-C_6H_3-2"-Me-4"-AsO_3H_2	372
NHC_6H_3-2'-OMe-4'-C_6H_3-2"-OMe-4"-AsO_3H_2	372
NHC_6H_4-4'-$CH_2C_6H_4$-4"-AsO_3H_2	372

R_6	R_8	Activity	References
AsO	NHCOMe	0	115
OMe	AsO_3HNa	sl.-birds C-human	115
OEt	AsO_3HNa	sl.-birds C-human	115
(7-AsO_3HNa)	NO_2	0	115
AsO_3HNa	OMe	0	115
	$NHCH_2CONHC_6H_4$-4'-AsO_3H_2		43
$NHCH_2CONHC_6H_4$-4'-AsO_3H_2			43
$NHCH_2CONHC_6H_4$-4'-AsO_3H_2	(2-Me)		43
(5-$NHCH_2CONHC_6H_4$-4'-AsO_3H_2)	OMe		43
(5-NO_2)	NHC_6H_4-2'-AsO_3H_2		373

Table 96

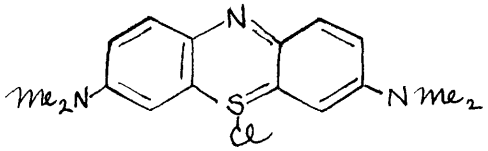
d. 3. Miscellaneous Compounds

Structure	Activity	References
		115
		115
		372
		373
	0	115

PART I. PHENOTHIAZINE DERIVATIVES

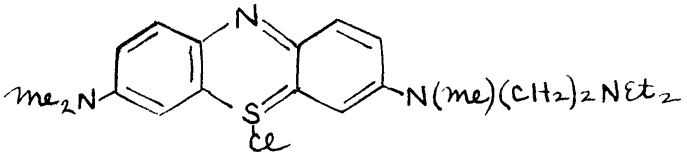
Discussion

One of the first compounds shown to possess antimalarial activity was methylene blue (XV). When one of the dimethyl amino groups



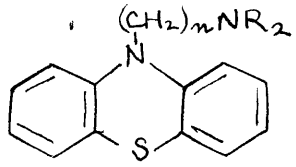
XV

was replaced with a 2-diethylaminoethyl methylamino group a compound (XVI) with greater activity was obtained. The activity of this compound may be



XVI

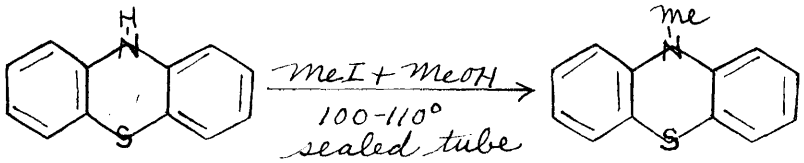
attributed to the combination of phenothiazine nucleus with the dialkylaminoalkylamino group. The dialkylaminoalkylamino group has been used with great success in producing active compounds of the quinoline and acridine series. It was thought of interest to prepare a compound of similar structure in which the nitrogen atom of the phenothiazine nucleus is connected to a dialkylaminoalkyl group as in formula XVII.



XVII

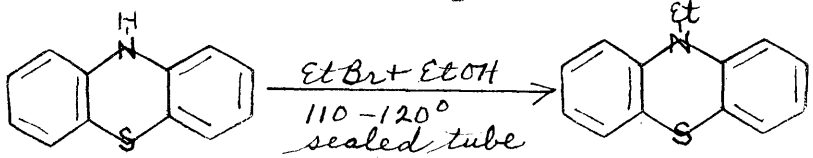
The preparation of N-substituted dialkylaminoalkyl phenothiazines was attempted by direct alkylation of phenothiazine by treatment with an appropriate substituted alkyl halide. Since the nitrogen atom

of phenothiazine is only very weakly basic it was expected that the reaction would proceed with difficulty. A survey of the methods of preparing N-alkyl phenothiazines revealed the fact that condensation may be effected by heating phenothiazine with an alkyl halide and a solvent in a sealed tube. Bernthsen (29) prepared N-methylphenothiazine (XVIII) by heating phenothiazine with methyl iodide and methanol at 100-110° in a sealed tube.



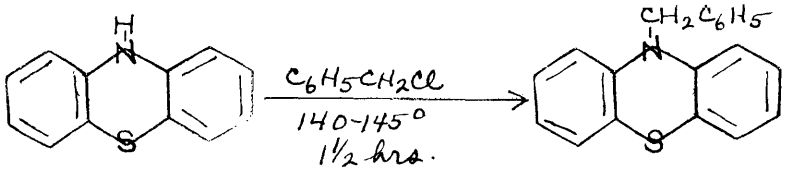
XVIII

N-Ethylphenothiazine (XIX) was similarly prepared (29), using ethyl bromide and ethanol and heating at 110-120°.



XIX

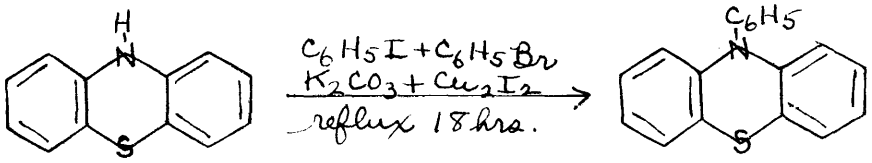
In the preparation of N-benzylphenothiazine (XX) the high boiling point of benzyl chloride precluded the necessity of a sealed tube. The reaction, described by Finzi (119), was performed at 140-145° for one and one-half hours, in the absence of a solvent.



XX

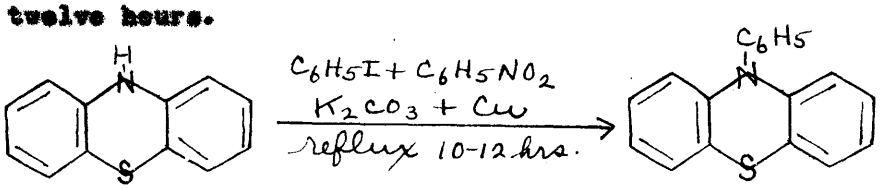
The direct arylation of phenothiazine, using an aryl halide, requires an alkaline condensing agent and a catalyst. Thus, N-phenylphenothiazine (XXI) was prepared by Barnett and Smiles (17) by refluxing

phenothiazine with iodobenzene for 18 hours in the presence of potassium carbonate and cuprous iodide, using bromobenzene as a solvent. Pinsi (119)

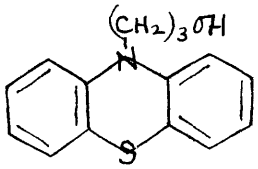


XXI

used nitrobenzene as a solvent in this same reaction and substituted copper powder for the cuprous iodide as a catalyst, refluxing for ten to twelve hours.

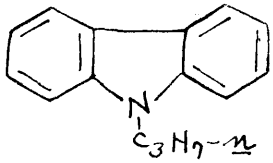


An attempt was made to prepare 10-(3'-hydroxypropyl)-phenothiazine (XXII) by refluxing phenothiazine and trimethylene chlorohydrin with potassium carbonate and copper powder in nitrobenzene for twenty-six hours. However, no product could be isolated.



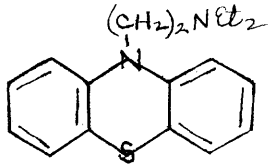
XXII

Stevens and Tucker (378) prepared N-n-propylcarbazole (XXIII) in 85 percent yield by refluxing for twelve hours a solution of carbazole, n-propyl iodide, and potassium hydroxide, in aqueous acetone.



XXIII

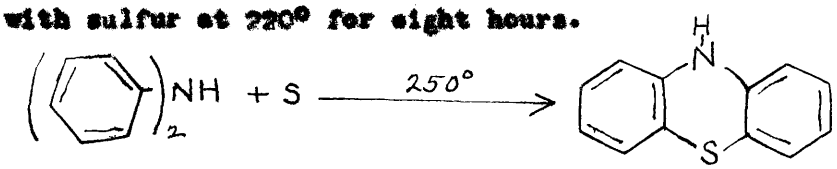
This same method was applied in an attempt to prepare 10-(2'-diethylaminoethyl)-phenothiazine (XXIV) by reacting phenothiazine with 2-diethylaminoethyl chloride but no condensation product could be isolated.



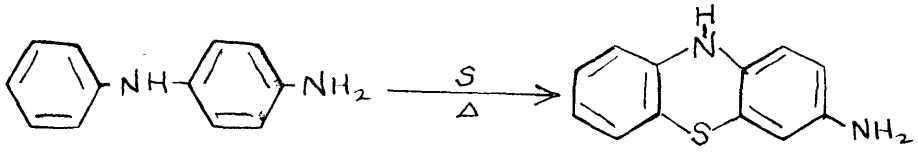
XXIV

The preparation of N-sodiophenothiazine was attempted with the view of reacting the sodio-derivative with an alkyl halide in order to prepare an N-alkylphenothiazine. Direct treatment of phenothiazine with sodium at 200-210° produced no reaction, and the subsequent addition of excess trimethylene chlorohydrin and further heating produced none of the desired 10-(3'-hydroxypropyl)-phenothiazine. A second attempt at preparation of N-sodiophenothiazine apparently was successful. In this case a boiling solution of phenothiazine in toluene was treated with sodium and after twelve hours the sodium had reacted and an orange suspension of the sodio-derivative had formed. Reaction of this product with 2-diethylaminoethyl chloride produced a substance which could not be induced to crystallize and which could not be distilled without decomposition.

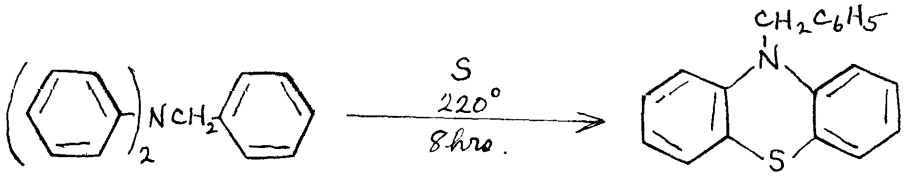
Phenothiazines have been prepared by heating diphenylamines with sulfur. When diphenylamine is heated with sulfur at 250° phenothiazine (XXV) is formed. Similarly, Bernthsen (30) heated 4-aminodiphenylamine with sulfur and obtained 3-aminophenothiazine (XXVI). Desai (86) prepared 10-benzylphenothiazine (XXVII) by heating N-benzyldiphenylamine with sulfur at 220° for eight hours.



XXV



XXVI



XXVII

Accordingly, the synthesis of desired N-substituted diphenylamines was undertaken with the view of subsequently reacting them with sulfur to produce 10-substituted phenothiazines.

Bischoff (91) prepared ethyl ∝-diphenylaminopropionate (XXVIII) in 96 percent yield by heating diphenylamine and ethyl ∝-bromopropionate at 170° for four hours. Desai (86) obtained a 94 percent yield

$$(C_6H_5)_2NH + BrCH(Me)CO_2Et \xrightarrow[4\ hrs.]{170^\circ} (C_6H_5)_2NCH(Me)CO_2Et$$

XXVIII

of N-benzyldiphenylamine (XXIX) by heating diphenylamine and benzyl chloride for ten hours with iodine and sodium acetate. Laum (226) prepared

$$(C_6H_5)_2NH + C_6H_5CH_2Cl \xrightarrow[10\ hrs.]{I_2 + NaOAc,\ 105\text{-}110^\circ} (C_6H_5)_2NCH_2C_6H_5$$

XXIX

methyl phenyl 3-hydroxypropylamine (XXX) by heating methylaniline and trimethylene chlorohydrin for forty to fifty hours at 120-130°.

$$C_6H_5NHMe + Cl(CH_2)_3OH \xrightarrow[40\text{-}50\ hrs.]{120\text{-}130^\circ} C_6H_5N(Me)(CH_2)_3OH$$

XXX

An attempt was made to prepare N-(3'-hydroxypropyl)-diphenylamine (XXXI) by heating diphenylamine with trimethylene chlorohydrin

$(C_6H_5)_2N(CH_2)_3OH$

XXXI

and ethanol in a sealed tube at 115-125° for two hours. However, only recovered starting materials were obtained.

The preparation of N-(2'-phenoxyethyl)-diphenylamine (XXXII) was attempted by heating diphenylamine and 2-phenoxyethyl bromide in a sealed tube at 195-205° for four hours. Vacuum distillation of the

$(C_6H_5)_2N(CH_2)_2OC_6H_5$

XXXII

reaction product yielded phenol, identified by boiling point, reaction with bromine water, and positive Liebermann's nitroso test. A second fraction, b.p. 165-220°/16 mm., and a third fraction, b.p. 140-143°/12 mm., were obtained. Fractions 2 and 3, when crystallised from ethanol, yielded colorless crystals which melted at 39° and 45° on the hot stage microscope.

Analysis: Found: C, 85.36; H, 6.87

C, 85.35; H, 6.78

Calculation for N-(2-phenoxyethyl)-diphenylamine, $C_{20}H_{19}ON$, gives C, 83.01; H, 6.62. Calculation for diphenylamine, $C_{12}H_{11}N$, gives C, 85.17; H, 6.55. This product yielded an acetyl derivative with m.p. 99-100°, causing no depression of the melting point of an authentic sample of N-acetyldiphenylamine, m.p. 99-100°. Therefore, the product obtained from the reaction was recovered diphenylamine. The N-acetyldiphenylamine was prepared according to Claus (71) by refluxing diphenylamine with acetic anhydride. The method was considerably improved by using a trace of concentrated sulfuric acid in the reaction.

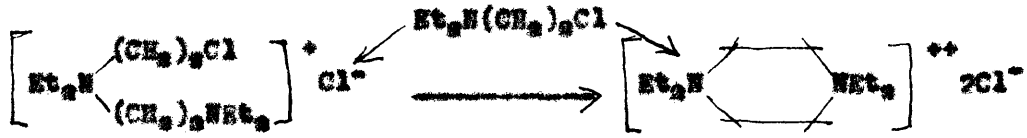
Trimethylene chlorohydrin was prepared according to "Organic Syntheses" (305) from trimethylene glycol and hydrogen chloride. The

copper powder catalyst was prepared from copper sulfate and zinc (308).

2-Diethylaminoethyl chloride was prepared by a series of reactions starting with the synthesis of diethylaniline from aniline, diethyl sulfate and calcium oxide (56). The diethylaniline was converted to p-nitrosodiethylaniline by treatment with nitrous acid using the directions in "Organic Syntheses" (307) for the preparation of p-nitrosodimethylaniline. The p-nitrosodiethylaniline was hydrolyzed with sodium hydroxide

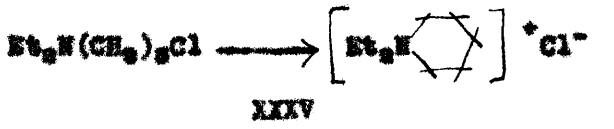
by the method of Koenigsberg (218) to produce diethylamine, and reaction of diethylamine with ethylene oxide according to Headlee, Collett and Lazzell (145) produced 2-diethylaminoethyl alcohol. This was converted to 2-diethylaminoethyl chloride by treatment with thionyl chloride, according to the directions of Sletta and Behmisch (274).

When the colorless, liquid 2-diethylaminoethyl chloride was allowed to stand it deposited colorless crystals which were insoluble in toluene, benzene, chloroform, and ether, but were soluble in water. The aqueous solution gave an immediate precipitate of silver chloride when treated with silver nitrate. This solid is probably the product of dimerization, either diethyl 2-chloroethyl 2'-diethylaminoethyl ammonium chloride (XXXIII) or 1,1,4,4-tetraethylpiperazinium dichloride (XXXIV).



XXXIII XXXIV

This is analogous to the spontaneous polymerization of 5-diethylaminopentyl chloride to 1,1-diethylpiperidinium chloride (XXXV) (274). In order to prevent further dimerization, the 2-diethylaminoethyl chloride



XXXV

was treated with dry hydrogen chloride to form the stable hydrochloride salt. An attempt was made to prepare 2-diethylaminoethyl alcohol by reacting monoethanolamine with ethyl iodide in the presence of potassium carbonate. However, no product was isolable. The ethyl iodide was prepared from diethyl sulfate, potassium iodide, and calcium carbonate (10).

2-Phenoxyethyl bromide was prepared according to Bentley, Haworth and Perkin (26) in 16 percent yield from sodium phenoxide and ethylene dibromide (prepared from ethylene and bromine). When the directions of "Organic Syntheses" (302) were followed a 47 percent yield was obtained.

N-Ethylphenothiazine was prepared in 59 percent yield by reacting phenothiazine with ethyl iodide in a sealed tube at 100-110° for one hour (29).

Trimethylene chlorohydrin was converted to γ-chloropropyl acetate in 89 percent yield by refluxing with glacial acetic acid and benzene in the presence of p-toluenesulfonic acid, continuously removing the water as it formed. Derick and Bissell (85) prepared this compound in 87 percent yield by reacting trimethylene chlorohydrin with acetyl chloride.

Experimental

Trimethylene Chlorohydrin. A 125-cc. Claisen flask with a sealed-on additional arm was fitted with a separatory funnel, a thermometer, and an inlet tube leading nearly to the bottom of the flask, and the delivery tube lead to a condenser set for downward distillation. A receiver consisting of a 500-cc. suction flask was attached tightly to the end of the condenser, and the side arm of the receiver was attached to a reflux condenser. A tube was led from the top of the condenser to a gas-absorption trap to take care of excess hydrogen chloride during the distillation. About 75-90 cc. of trimethylene glycol was placed in the flask and heated by means of a metal bath to 150-170°. A very rapid stream of dry hydrogen chloride (from a 5-l. flask half-filled with a paste of salt and concentrated hydrochloric acid and fitted with a delivery tube and dropping funnel of concentrated sulfuric acid) was then led into the hot glycol through the inlet tube. A reddish distillate consisting of water, trimethylene chlorohydrin, hydrogen chloride, and some unchanged glycol began to distil. As rapidly as the glycol was used up in the reaction flask, more was added from the separatory funnel. The amount of material in the reaction flask was kept as small as possible. The hydrogen chloride was passed in at such a rate that 2-3 cc. of trimethylene glycol were used up in one minute. The weight of crude distillate from 300 g. of trimethylene glycol was 486 g.

To obtain the trimethylene chlorohydrin, the distillate from this operation was heated for about one hour on a steam bath, under reflux, in order to drive out most of the excess hydrogen chloride. The distillate was then fractionated under reduced pressure in a modified Claisen flask with 25-cm. fractionating side arm. The fractions collected under 10 mm.

were: to 55°, 55-57°, 57-65°, 65-85°, 85-105°, residue.

Before a further fractionation was carried out, the residue was discarded; the portion boiling at 85-105°, consisting of unchanged trimethylene glycol, was set aside; the low boiling portion up to 55°, consisting mainly of water and hydrogen chloride with some trimethylene chloride and trimethylene chlorohydrin, was neutralised carefully with powdered sodium carbonate. Two layers formed and the upper containing the chlorohydrin was separated, dried over anhydrous potassium carbonate and again replaced as the portion boiling up to 55°. Another complete fractional distillation was carried out on the fractions boiling up to 85°, and the following fractions were collected under 10 mm.: to 55°, 55-60°, 60-64°, 64-85°.

The final yield of trimethylene chlorohydrin boiling at 60-64°/10 mm. was 185 g. from 300 g. of trimethylene glycol (64 percent of the theoretical amount), and 67 g. of trimethylene glycol was recovered.

Copper Powder. One hundred grams (0.4 mole) of copper sulfate pentahydrate was dissolved in 350 cc. of hot water in a 1-l. beaker. After cooling to room temperature 35 g. (0.53 atom) of zinc dust was gradually added, with stirring, until the solution was decolorized. The precipitated copper was washed by decantation with water. Dilute hydrochloric acid (5 percent) was added to the precipitate to remove the excess of the zinc, and agitation was continued until the escape of hydrogen ceased. The copper powder was washed by decantation with water, and kept under water in a glass stoppered bottle.

Attempted Synthesis of 10-(3'-Hydroxypropyl)-phenothiazine. Trial 1. In a 200-cc. glass-jointed flask, fitted with a reflux condenser, were placed 5 g. (0.025 mole) of phenothiazine, 4.7 g. (0.05 mole) of trimethylene chlorohydrin, 6.9 g. (0.05 mole) of dry powdered potassium

carbonate, 55 cc. of nitrobenzene, and 0.5 g. of copper powder. The mixture was refluxed for twenty-six hours. The red-brown mixture was steam-distilled to remove the nitrobenzene, leaving a brown residue which solidified on cooling. The aqueous layer was decanted and the residue was extracted with boiling ethanol. The ethanol solution was boiled with Norit, filtered, and allowed to stand. However, the solution could not be induced to crystallize. The ethanol was distilled off and the dark brown residue was distilled in vacuo, but decomposition occurred and no distillate was obtained.

Diethylaniline. To 93 g. (1 mole) of aniline in a 1-l. three-necked flask, equipped with a Hershberg stirrer, reflux condenser, and a thermometer reaching to within 1 cm. of the bottom of the flask, was added 89 g. (1.2 moles) of dry powdered calcium hydroxide. To this stirred mixture was added 206 g. (1.4 moles) of diethyl sulfate in five portions over a period of forty-five minutes. The temperature rose after each addition of the diethyl sulfate and cooling was partially effected by applying an ice bath. The mixture became very thick at the beginning of the reaction and stirring was sporadic. Thus, it was impossible to control the temperature and consequently the temperature rose much above 85° several times. The reaction was then heated at a bath temperature of 155° for four hours, with inefficient stirring, but the temperature within the reaction vessel never rose above 110°. The mixture was steam-distilled, and the amine layer in the distillate was separated, dried over solid potassium hydroxide, and distilled. The diethylaniline distilled at 95°/12 mm., and weighed 143 g. (96 percent of the theoretical amount).

The synthesis was repeated on a larger scale under more controlled conditions. To 279 g. (3 moles) of aniline in a 1-gallon

iron jacketed autoclave, fitted with a plow stirrer, reflux condenser 25 cm. long leading to a downward condenser, thermometer well, and dropping funnel, was added 246 g. (3.6 moles) of dry powdered calcium hydroxide. The mixture was stirred and to this five portions of diethyl sulfate, totalling 618 g. (4.2 moles), were added at intervals of ten minutes. Ice water was circulated through the jacket of the autoclave, and the temperature of the reaction was kept below 60°. After the final heat rise had begun to subside the autoclave was heated by passing steam under pressure through the jacket until the temperature of the reaction mass was 110-115°. The vapors which passed through the reflux condenser were collected, the water separated off, and the amine layer returned to the reaction. The mixture was heated for four hours with high pressure (100 pounds) steam. Two liters of water were added to the reaction mixture after cooling, and then the mixture was steam-distilled. The distillate yielded 975 cc. of wet crude diethylaniline. The contents of the autoclave was treated with dilute hydrochloric acid, filtered, and the filtrate concentrated. The resulting solution was made alkaline with potassium hydroxide, steam-distilled, and the amine fraction in the distillate separated. The combined amine fractions were dried over solid potassium hydroxide and distilled. The diethylaniline boiled at 95°/19 mm., and weighed 379 g. (85 percent of the theoretical amount).

p-Nitrosodiethylaniline. A solution of 358 g. (2.4 moles) of diethylaniline in 1050 cc. of concentrated hydrochloric acid was placed in an 8-l. Pyrex battery jar, surrounded with ice, and finely divided ice was added until the temperature had fallen to 5°. The contents of the jar was stirred mechanically and a solution of 180 g. (2.6 moles) of sodium nitrite in 900 cc. of water was slowly added from a

separatory funnel, the stem of which dipped beneath the surface of the liquid. The addition took one hour and the temperature was kept below 8° by adding ice. When all the nitrite had been added the mixture was allowed to stand for one hour and 1500 cc. of a cold solution of 430 g. of sodium hydroxide was added with stirring and addition of ice until the mixture was alkaline. A voluminous dark blue-green crystalline precipitate formed. The mixture was allowed to stand in ice for one hour and then filtered through a Buchner funnel and the crystals air dried. The p-nitrosodiethylaniline weighed 421 g. (98 percent of the theoretical amount).

Diethylamine. The apparatus consisted of a 12-l. flask fitted with a dropping funnel, mechanical stirrer, and an efficient condenser (copper tube cooled with ice water) leading to a 5-l. flask, cooled in an ice bath, and fitted with a Dimroth condenser set for reflux. The top of this condenser lead to a trap containing concentrated hydrochloric acid. Ice water was circulated through the condensers. A solution of 400 g. (10 moles) of sodium hydroxide in 6 l. of water was added to the 12-l. flask and heated with an oil bath at 120°. While stirring, a solution of 400 g. (2.2 moles) of p-nitrosodiethylaniline and 237 cc., 280 g. (2.8 moles) of concentrated hydrochloric acid in enough water to make 2.5 l. was added through the dropping funnel over a period of two hours. The distillate of diethylamine was yellow. The diethylamine distillate was purified by distilling it from solid sodium hydroxide. A 2-l. three-necked glass-jointed flask was fitted with a stirrer, dropping funnel with gas inlet, and a goose neck leading to a 500 cc. Claisen flask containing a few boiling chips and heated to 70° by a water bath and equipped with a thermometer. The Claisen flask led to a Liebig condenser set for downward distillation and leading to a 1-l. two-necked glass-jointed flask, cooled

in an ice bath, the other neck of which was fitted with a Friedrich condenser set at reflux, the top leading to a trap containing hydrochloric acid. The gas inlet tube of the dropping funnel led nearly to the bottom of the 2-l. flask. Sodium hydroxide pellets, 200 g., were introduced into the 2-l. flask and the crude diethylamine solution was added through the dropping funnel all at once. The mixture was stirred and heated with an oil bath at 90°. The diethylamine distilled over water-white at 56°. Near the end of the distillation air was slowly bubbled through the contents of the 2-l. flask to remove the remainder of the diethylamine. The distillation was stopped when yellow N-nitrosodiethylamine distilled into the Claisen flask. The weight of pure diethylamine was 125 g. (78 percent of the theoretical amount).

2-Diethylaminoethyl Alcohol. In a steel bomb of 750 ml. capacity were placed 38.3 g. (0.53 mole) of diethylamine and 23.5 g. (0.53 mole) of ethylene oxide. The bomb was sealed and heated in an oil bath at 100° for one hour. The bomb was cooled and the contents washed out with ether. The amber liquid was fractionally distilled in a modified Claisen flask, first at atmospheric pressure to remove the ether and unreacted ethylene oxide and diethylamine, and then at 75 mm. The fraction boiling at 94-95°/75 mm. was collected as 2-diethylamino-ethyl alcohol, weighing 48.2 g. (78 percent of the theoretical amount).

In a 500-ml. three-necked glass-jointed flask, fitted with a dropping funnel, efficient mercury-sealed stirrer, and Friedrich condenser set at reflux, were placed 30.5 g. (0.5 mole) of monoethanolamine and 83 g. (0.6 mole) of potassium carbonate. The mixture was stirred and 209 g. (1.3 moles) of ethyl iodide was added through the dropping funnel in five portions while cooling the flask in an ice bath. After the initial vigorous reaction, the mixture was heated with an oil bath

up to 100° for half an hour, while stirring. After cooling, 100 cc. of ether was added and brought to reflux for ten minutes. To this was added 300 ml. of water and the ether layer was separated. The aqueous layer was extracted with three 100-ml. portions of ether. The combined ether extracts were carefully evaporated to remove the ether, but only a very small amount of liquid residue remained.

2-Diethylaminoethyl Chloride. To a solution of 48.9 g. (0.38 mole) of 2-diethylaminoethyl alcohol in 475 cc. of benzene was carefully added, with cooling, 95 g. (0.80 mole) of thionyl chloride (distilled from 3 percent of linseed oil). A crystalline precipitate immediately formed, sulfur dioxide was evolved, and much heat was generated. The mixture was refluxed for two hours, and the benzene and excess thionyl chloride removed by distillation. The crystalline residue was crystallized from ethanol-benzene, yielding 68 g. of air-dried product. The hydrochloride salt was dissolved in a little water, cooled with ice, and treated with 200 cc. of a saturated solution of sodium carbonate, causing two layers to form. The aqueous layer was basic to Congo red. The 2-diethylaminoethyl chloride was extracted with three 200-cc. portions of ether and the ether extract was dried over sodium sulfate and sodium carbonate. The ether was removed by careful distillation and the 2-diethylaminoethyl chloride was distilled in a modified Claisen flask, yielding a colorless liquid boiling at 78°/75 mm., weighing 44 g. (86 percent of the theoretical amount).

After standing for one month the liquid had deposited colorless crystals which were removed by filtration. The unchanged 2-diethylaminoethyl chloride was dissolved in dry toluene and treated with dry hydrogen chloride, forming a colorless precipitate of 2-diethylaminoethyl chloride hydrochloride.

The solid which had crystallized from the 2-diethylaminoethyl chloride was insoluble in ether, toluene, benzene, and chloroform, but was soluble in water. When the aqueous solution was treated with aqueous silver nitrate a precipitate of silver chloride was immediately formed. This solid is either diethyl 2-chloroethyl 2'-diethylaminoethyl ammonium chloride (XXXIII), or 1,1,4,4-tetraethylpiperazinium dichloride (XXXIV).

Attempted Synthesis of 10-(2'-Diethylaminoethyl)-phenothiazine, Trial 1. In a 500-cc. glass-jointed flask were placed 14 g. (0.07 mole) of phenothiazine, 9.5 g. (0.07 mole) of 2-diethylaminoethyl chloride, 2.7 g. (0.07 mole) of potassium hydroxide dissolved in 5 cc. of water, and 50 cc. of acetone. The mixture was refluxed for twelve hours. The acetone was distilled off and the residue was triturated with dry benzene and filtered. The precipitate of potassium chloride was washed with a little dry benzene and the combined benzene solutions were treated with dry hydrogen chloride, causing the precipitation of a dark colored product. The precipitate was removed by filtration and heated on a steam bath with 75 cc. of concentrated hydrochloric acid and 75 cc. of water. To this was added enough water to form a 10 percent hydrochloric acid solution. The dark-green insoluble solid was removed by filtration and the reddish filtrate was concentrated in vacuo. After removing 210 cc. of distillate the residual brown liquid was cooled and treated with 200 cc. of 10 percent potassium hydroxide solution producing an alkaline solution which was nearly colorless and containing only a very small amount of precipitate. The precipitate proved to be too small in amount for further characterization.

Attempted Synthesis of 10-(3'-Hydroxypropyl)-phenothiazine, Trial 2. In a 200-cc. two-necked glass-jointed flask, fitted with a reflux condenser closed with a drying tube, dropping funnel and gas inlet,

was placed 9.96 g. (0.05 mole) of phenothiazine. The flask was swept with nitrogen and 1.15 g. (0.05 atom) of sodium was added. The flask was heated to 200-210° with an oil bath and the contents of the flask melted. Heating was continued for 30 minutes with occasional agitation but no reaction was observed. The flask was cooled and 9.45 g. (0.10 mole) of trimethylene chlorohydrin was introduced through the dropping funnel. The flask was heated slowly with an oil bath until all the sodium had reacted with the trimethylene chlorohydrin and then the temperature of the bath was raised to 185° and the mixture was refluxed for one hour. On cooling the mixture solidified. Ethanol was added and the solid brought into solution. Norit was added, and the mixture was refluxed and then filtered. The brown filtrate was concentrated at reduced pressure. The residue was crystallized from ethanol-water, yielding tan crystals. Fractional crystallization of this product from ethanol-water yielded three fractions which were recrystallized from benzene to form pale yellow crystals. Fraction 1, m.p. 175-180°, gave a mixed melting point of 175-180° with phenothiazine, m.p. 181-182°. Fraction 2, m.p. 177-180°, gave a mixed melting point of 178-181° with phenothiazine, m.p. 181-182°. Fraction 3, m.p. 177.5-180°, gave a mixed melting point of 178-181° with phenothiazine, m.p. 181-182°. Therefore these fractions were recovered phenothiazine.

Attempted Synthesis of 10-(2'-Diethylaminoethyl)-phenothiazine, Trial 2. In a 200-cc. two-necked glass-jointed flask, fitted with a mercury-sealed stirrer and reflux condenser, were placed 11.5 g. (0.057 mole) of phenothiazine and 100 cc. of dry toluene. The solution was refluxed, stirred vigorously, and 1.3 g. (0.057 atom) of sodium was added in small pieces through the top of the condenser. Refluxing and stirring was continued for twelve hours. At this time the sodium had

reacted and an orange suspension had formed. The top of the condenser was swept with nitrogen and 7.7 g. (0.057 mole) of 2-diethylaminoethyl chloride dissolved in 10 cc. of dry toluene was added through the top of the condenser. The orange color of the reaction was immediately dispelled and a dark color appeared. Refluxing and stirring was continued for three and a half hours. After cooling, the solution was filtered through a sintered glass funnel and the filtrate was extracted with 100 cc. of 10 percent hydrochloric acid. The aqueous solution was freed from toluene, cooled, and made alkaline with potassium carbonate, causing an oil to separate. The oil was extracted with ether, the ether extract was dried over sodium sulfate and potassium carbonate, and then saturated with dry hydrogen chloride. A white opalescence developed and then a deep green viscous liquid separated. Attempts to crystallize the oil were fruitless. The oil was treated with potassium carbonate solution, extracted with ether, and the ether extract subjected to vacuum distillation, but the product decomposed.

Ethyl Iodide. In a 12-l. flask, fitted with a dropping funnel, Hershberg stirrer, and fractionating column leading to an efficient condenser dipping into ice in a receiving flask, were placed a solution of 6640 g. (40 moles) of potassium iodide in 4 l. of water and 520 g. of calcium carbonate. The mixture was vigorously stirred and heated in an oil bath at 120°. Through the dropping funnel was added 6 l. (45 moles) of diethyl sulfate at such a rate that ethyl iodide distilled rapidly. The ethyl iodide was washed three times with cold water, yielding 9 l. of crude product (93 percent of the theoretical amount). The crude ethyl iodide was dried with Drierite, filtered, and fractionally distilled from phosphorous pentoxide and solid potassium iodide.

N-Ethylphenothiazine (XIX). Five grams (0.025 mole) of phenothiazine, 15.6 g. (0.1 mole) of ethyl iodide, and 25 cc. of ethanol, were heated in a sealed tube at 100-110° for one hour. Recrystallization of the product from ethanol yielded 1.93 g. of N-ethylphenothiazine as pale yellow needles, m.p. 101-102°. From the mother liquor 2.11 g. of phenothiazine was recovered. Based on phenothiazine consumed, the yield of N-ethylphenothiazine was 59 percent of the theoretical amount.

Attempted Synthesis of N-(3'-Hydroxypropyl)-diphenylamine. A mixture of 5.07 g. (0.03 mole) of diphenylamine, 3.8 g. (0.04 mole) of trimethylene chlorohydrin, and 25 cc. of ethanol, was heated in a sealed tube at 115-125° for two hours. The product, a purple liquid, was distilled in a modified Claisen flask at atmospheric pressure to remove the ethanol, and then at 2 mm. The first fraction, b.p. 90°/2 mm., weighing 3.0 g., was trimethylene chlorohydrin (79 percent recovery); and the second fraction, a pale yellow solid, b.p. 120-125°/2 mm., weighing 4.76 g. was diphenylamine (94 percent recovery).

Ethylene Dibromide. Ethylene was bubbled into 480 g. (3 moles) of bromine in a gas washing bottle cooled in an ice bath, until the bromine was all reacted. The crude ethylene dibromide was washed with two 100-cc. portions of sodium sulfite solution, and then with three 200-cc. portions of water. The ethylene dibromide was dried over anhydrous calcium chloride for twenty-four hours, dried over phosphorous pentoxide, and finally distilled from phosphorous pentoxide. The yield of water-white product was 445 g. (79 percent of the theoretical amount).

2-Phenoxyethyl Bromide. To 500 cc. of ethanol in a 1-l. glass-jointed flask fitted with a reflux condenser was added 23 g. (1 atom) of sodium, cut in small pieces. After all the sodium had dissolved, 94.1 g.

(1 mole) of phenol and 176 g. (1 mole) of ethylene dibromide was added. The solution was refluxed on a steam bath for three hours. The top of the condenser was connected to a water trap to absorb any vinyl bromide evolved. The ethanol was distilled from the mixture and 250 cc. of water was added and the mixture was warmed until the potassium chloride dissolved. The product was extracted with 600 cc. of ether, and the ether solution was freed from phenol by washing with 500 cc. of ten percent potassium hydroxide solution and then with 200 cc. of water. The ether solution was dried over calcium chloride and then the ether was removed by distillation. The residual liquid was distilled in a modified Claisen flask, and the colorless liquid boiling at 123°/17 mm. collected, weight 32.5 g. (16 percent of the theoretical amount).

The preparation was repeated in better yield by the following procedure: In a 1-l. three-necked glass-jointed flask, fitted with a Dimroth condenser, mercury-sealed stirrer, and dropping funnel, were placed 235 cc. of water, 235 g. (1.25 moles) of ethylene dibromide, and 94 g. (1 mole) of phenol. The mixture was stirred and heated to boiling, and 45 g. (1.12 moles) of sodium hydroxide in 120 cc. of water was added over a period of 20 minutes. The mixture was refluxed for five hours longer to complete the reaction, then cooled, and the upper water layer separated and discarded. The lower layer, consisting of ethylene dibromide, 2-phenoxyethyl bromide, and 1,2-diphenoxyethane, was distilled in a modified Claisen flask under reduced pressure. The first fraction was collected up to 125°/18 mm. and consisted of water, recovered ethylene dibromide, and a little phenoxyethyl bromide. The next fraction, b.p. 125-126°/18 mm., was collected as pure 2-phenoxyethyl bromide. The yield was 94.9 g. (47 percent of the theoretical amount). The residue was dissolved in ethanol, boiled with Norit, filtered and the filtrate was

concentrated. Colorless crystals of 1,2-diphenoxyethane were obtained, weighing 31.2 g.

Attempted Synthesis of N-(2'-Phenoxyethyl)-diphenylamine. A mixture of 16.92 g. (0.1 mole) of diphenylamine and 10.05 g. (0.05 mole) of 2-phenoxyethyl bromide was heated in a sealed tube at 195-205° for four hours. The brown viscous product was washed out with ethanol, the ethanol was distilled off, and the residue was triturated with water and extracted with benzene. The benzene solution was distilled in a modified Claisen flask, first at atmospheric pressure to remove the benzene, and then under reduced pressure. The first fraction was a colorless solid, b.p. 80-81°/16 mm., having the odor of phenol. It gave a positive Liebermann's nitroso test, was soluble in water, and reacted with bromine-water to give a colorless precipitate. Therefore, it was phenol. The second fraction was collected over the range of 165-220°/16 mm., and weighed 9.8 g. A third fraction boiled at 140-143°/12 mm., and weighed 2.0 g. The residue was a tar. Fractions 2 and 3 were combined and crystallized from ethanol, yielding 3.7 g. of colorless crystals, m.p. 39° and 45° on the hot stage microscope. The mother liquor yielded 3.7 g. of crystals.

Analysis: Calc'd for $C_{20}H_{19}ON$: C, 83.01; H, 6.62
Calc'd for $C_{18}H_{15}N$: C, 85.17; H, 6.55
Found: C, 85.96; H, 6.87
C, 85.35; H, 6.78

The analysis suggested that fractions 2 and 3 consisted of recovered diphenylamine. The acetyl derivative was prepared by refluxing 1.0 g. of the compound with 2.5 cc. of acetic anhydride and a trace of concentrated sulfuric acid, and then shaking with water. The crystalline

product was recrystallised from ethanol-water, yielding colorless plates, m.p. 95-98°. Recrystallization again from ethanol-water yielded colorless plates, m.p. 99-100°. The acetyl derivative caused no depression of the melting point of N-acetyldiphenylamine, m.p. 99-100°.

N-Acetyldiphenylamine. To 2.0 g. of diphenylamine was added 1.2 cc. of acetic anhydride and the solution was refluxed for 90 minutes. After cooling, 25 cc. of cold water was added and the mixture allowed to stand at room temperature. No crystals formed, but, after twelve hours, violent agitation caused the oil to solidify and crystals appeared.

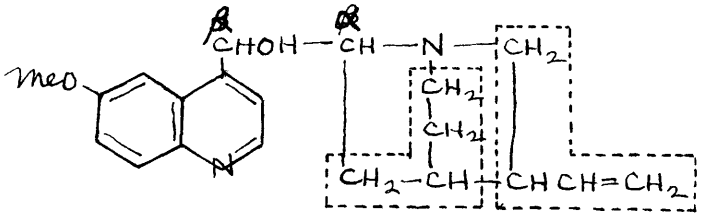
To 2.0 g. of diphenylamine were added 5 cc. of acetic anhydride and a trace of concentrated sulfuric acid. The solution was refluxed for one hour and twenty minutes. After cooling, 30 cc. of water was added and after shaking crystals formed. The product was washed with water and crystallized from ethanol-water, yielding colorless crystals of N-acetyldiphenylamine, m.p. 99-100°.

γ-Chloropropyl Acetate. To 37 g. (0.4 mole) of trimethylene chlorohydrin in a 200-ml. glass-jointed flask were added 24 g. (0.4 mole) of glacial acetic acid, 1 g. of p-toluenesulfonic acid, and 100 cc. of benzene. The mixture was refluxed into a moisture-point receiver until no more water was collected (7.8 cc. in one hour). The mixture was distilled in a modified Claisen flask, and the fraction boiling at 170-172° collected, weighing 45.2 g. (83 percent of the theoretical amount).

PART II. DIPHENYLAMINE DERIVATIVES

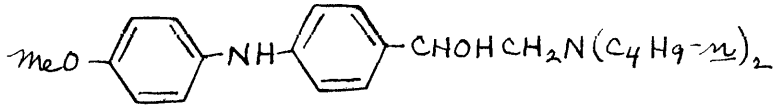
Discussion

Examination of the structure of quinine (XXXVI) reveals that the molecule contains a weakly basic nitrogen (in the quinoline nucleus), a strongly basic nitrogen (in the quinuclidine ring), a secondary alcoholic hydroxyl group in a position beta to the strongly basic nitrogen atom, and a methoxy group in a position para to the weakly basic nitrogen atom. Further examination reveals that the quinuclidine portion of the molecule may be considered as a di-n-butyl-substituted amine.



XXXVI

It was thought desirable to prepare a compound embodying these components, but without incorporating the quinoline and quinuclidine rings. 4-Methoxy-4'-(β-di-n-butylamino-α-hydroxyethyl)-diphenylamine (XXXVII) would include these specified parts.



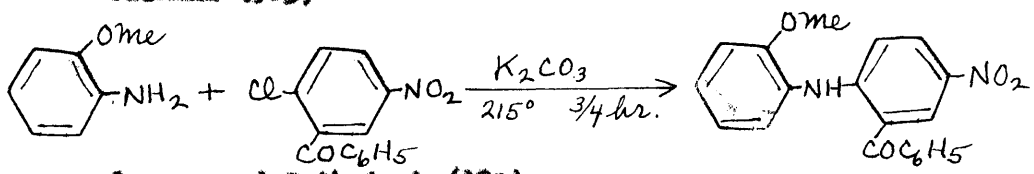
XXXVII

The synthesis of a compound of this type could be approached by condensation of anisidine with α-(p-bromophenyl)-β-dialkylamino-ethanol. The synthesis could also be approached through the preparation of 4-acetyl-4'-methoxydiphenylamine, and subsequent building up of the alkanolamine sidechain by bromination, amination, and reduction:

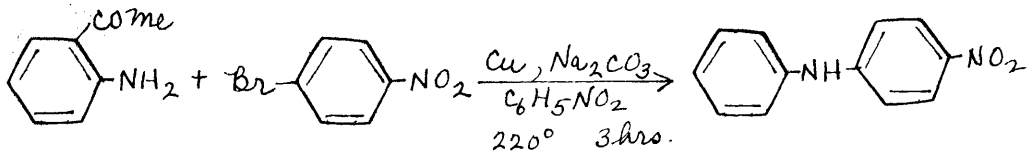
$-COMe \longrightarrow -COCH_2Br \longrightarrow -COCH_2NR_2 \longrightarrow -CHOHCH_2NR_2$

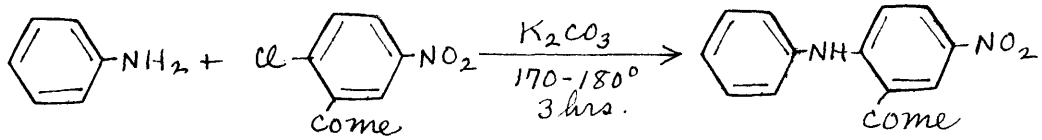
The condensations between substituted anilines and substituted aryl halides are generally effected by heating in nitrobenzene, amyl alcohol, or an excess of one of the reactants, with a catalyst, such as copper powder or cuprous iodide, and an alkaline condensing agent, such as potassium carbonate. If the aryl halide has a labilized halogen, as in the case of negatively-substituted aryl halides, the catalyst is sometimes omitted. The following examples will serve to illustrate the synthesis of substituted diphenylamines.

Ullmann (305):

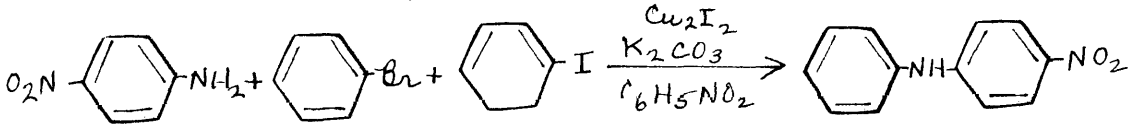


Jensen and Rothwisch (197):

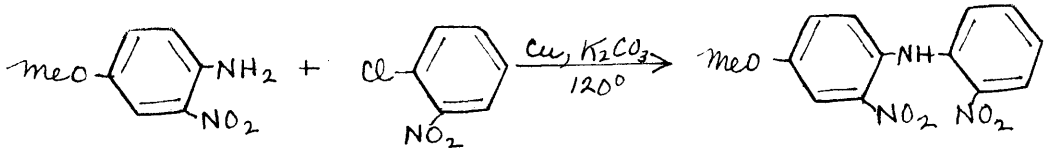




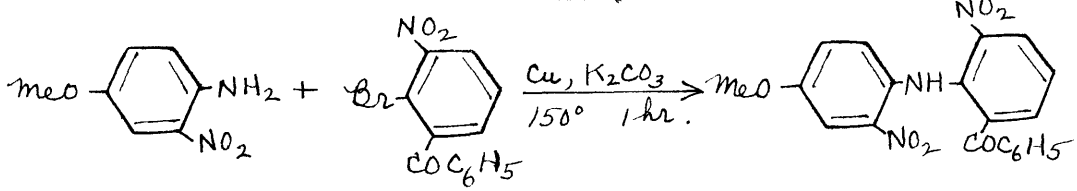
Sissoeff (370):

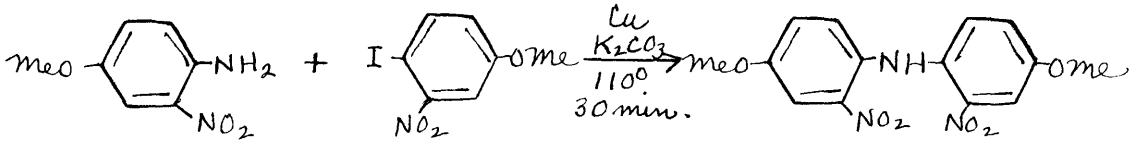


Tomlinson (384):

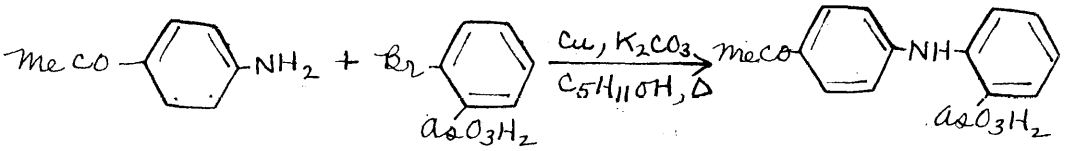


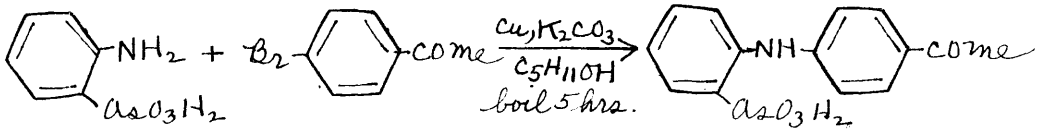
Robinson and Tomlinson (328):





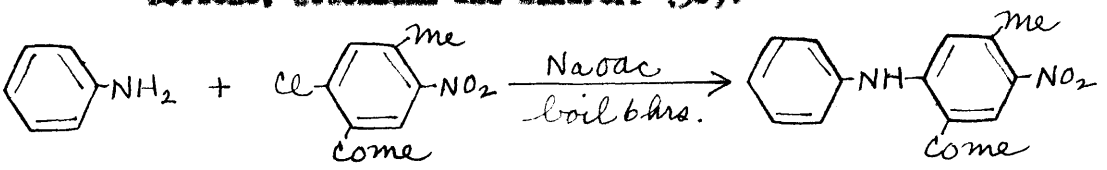
Gibson and Levin (128):

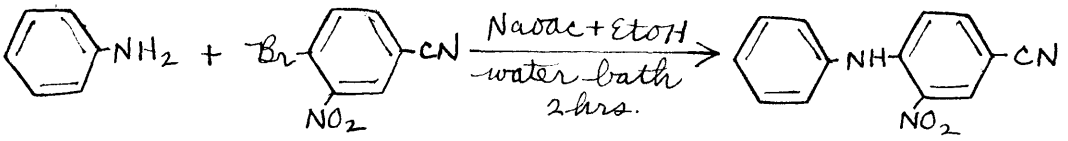




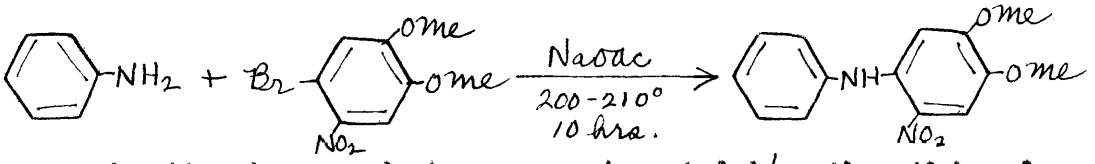
Negatively-substituted aryl halides have been condensed with aniline by heating with sodium acetate.

Borsche, Steckmann and Makaroff (38):





Hughes, Lions, Maumsell and Wright (155):

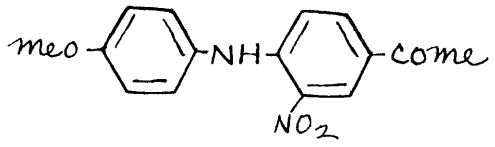


An attempt was made to prepare 4-acetyl-4'-methoxydiphenylamine by heating a mixture of p-anisidine, p-bromoacetophenone, potassium carbonate, copper powder, and nitrobenzene, at 215-220° for six hours. The product, after distillation, could not be purified. The preparation was repeated, using a mixture of copper powder and cuprous iodide as catalyst, and heating at 200° for three hours. Sublimation of the product in vacuo yielded an orange sublimate which, when repeatedly crystallized

from ethanol, yielded yellow crystals which sintered at 159-160° and melted at 175-185°. The analysis of this product was not in agreement with that calculated for 4-acetyl-4'-methoxydiphenylamine.

An attempt to prepare 4-acetyldiphenylamine, by heating a mixture of aniline, p-bromoacetophenone, potassium carbonate, nitrobenzene, and copper powder, at 200° for three hours, yielded a product which could not be purified.

4-Acetyl-2-nitro-4'-methoxydiphenylamine (XXXVIII) was



XXXVIII

prepared by heating a mixture of 3-nitro-4-bromoacetophenone, p-anisidine, and sodium acetate, at 150° for six hours. The compound was obtained in impure form as chocolate brown crystals from ethanol, m.p. 188-190°. Repeated recrystallization from ethanol did not improve the purity of the product.

Cuprous iodide was prepared from copper sulfate, potassium iodide, and sodium thiosulfate.

3-Nitro-4-bromoacetophenone was prepared in 57 percent yield according to Borsche, Steinmann and Makaroff (38) by nitrating p-bromoacetophenone.

Experimental

Attempted Preparation of 4-Acetyl-4'-methoxydiphenylamine.

Trial 1. In a 1-l. two-necked glass-jointed flask fitted with a mercury-sealed stirrer and reflux condenser, the top of which led to a downward condenser, were placed 49.2 g. (0.4 mole) of p-anisidine, 79.6 g. (0.4 mole) of p-bromoacetophenone, 55.2 g. (0.4 mole) of powdered anhydrous potassium carbonate, 0.5 g. of copper powder, and 275 cc. of nitrobenzene. The mixture was stirred and heated in a metal bath at 215-220° for six hours. The reflux condenser was kept just cool enough so that the nitrobenzene refluxed near the top and water from the reaction slowly distilled over into the downward condenser. The reaction mixture was cooled, 250 cc. of water was added, and the mixture was steam-distilled until the nitrobenzene was removed and a solid collected in the condenser. The residual liquid was cooled and a black mass solidified. The aqueous layer was decanted and the black residue was taken up in 2.5 l. of benzene. The benzene solution was washed with two 300-cc. portions of 10 percent hydrochloric acid, one 300-cc. portion of water, two 300-cc. portions of 5 percent sodium bicarbonate, and finally with one 300-cc. portion of water. The benzene solution was filtered and dried by refluxing into a moisture-point receiver. The dried benzene solution was filtered to remove a small quantity of black solid. The solution was saturated with dry hydrogen bromide and a dark brown solid separated. The solid was removed by filtration and crystallized from absolute ethanol, but no purification was effected. Most of the ethanol was distilled off, water was added to the residue, and the distillation was continued until the remainder of the ethanol had been removed. A black solid, weighing 26.3 g., was removed by filtration. This solid was distilled in a sausage flask at

1 mm. The distillate consisted of a yellow solid and then a brown solid, b.p. up to 250° with bath temperature up to 300°. The residue in the flask was a black brittle solid. Attempts to purify the distillate were futile.

Cuprous Iodide. A solution of 24.79 g. (0.1 mole) of copper sulfate pentahydrate was added to a solution of 16.60 g. (0.1 mole) of potassium iodide and 24.82 g. (0.1 mole) of sodium thiosulfate pentahydrate. The solutions were mixed while hot and the nearly colorless precipitate of cuprous iodide was removed by filtration and washed with water. The precipitate weighed 19.0 g. (100 percent of the theoretical amount) after being dried in an oven.

Attempted Preparation of 4-Acetyl-4'-methoxydiphenylamine, Trial 2. In a 500-cc. three-necked glass-jointed flask fitted with a mercury-sealed stirrer, reflux condenser, and downward condenser, were placed 19.9 g. (0.1 mole) of p-bromoacetophenone, 12.3 g. (0.1 mole) of p-anisidine, 13.8 g. (0.1 mole) of powdered anhydrous potassium carbonate, 0.1 g. of cuprous iodide, 0.1 g. of copper powder, and 100 cc. of nitrobenzene. The mixture was stirred and heated in a metal bath at 200° for three hours. Water and nitrobenzene distilled out, the water was separated, and the nitrobenzene was replaced. The mixture was steam-distilled to remove volatile materials and at the end of the distillation unreacted p-bromoacetophenone collected in the condenser. The residue was a hard black solid. The black residue was sublimed in vacuo at 1 mm. and 125° bath temperature and a yellow crystalline material collected on the cold finger. The sublimation was continued at 7 x 10^{-3} mm. and 200° bath temperature for forty-two hours. An orange sublimate collected on the cold finger. The sublimate was crystallized from ethanol, yielding yellow

crystals, sintering at 145° and melting at 150-170°. Recrystallization gave yellow crystals, sintering at 156° and melting at 158-186°. Two more recrystallizations did not change this melting behavior. Repeated recrystallization from ethanol yielded crystals which sintered at 159-160° and formed a clear melt at 175-188°.

Analysis:* Calc'd for $C_{19}H_{19}O_2N$: C, 74.66; H, 6.27

Found: C, 69.40; H, 5.00

C, 69.80; H, 4.85

C, 69.58; H, 4.95

The analysis of the compound was not in agreement with that calculated for 4-acetyl-4'-methoxydiphenylamine.

Attempted Preparation of 4-Acetyldiphenylamine. In a 500-cc. three-necked glass-jointed flask fitted with a mercury-sealed stirrer, reflux condenser, and downward condenser, were placed 9.82 g. (0.04 mole) of aniline, 7.96 g. (0.04 mole) of p-bromoacetophenone, 5.43 g. (0.04 mole) of anhydrous potassium carbonate, 100 cc. of nitrobenzene, and a small amount of copper powder. The mixture was stirred and heated with a metal bath for three hours at 200°. The water which formed in the reaction distilled off, together with a little nitrobenzene. The mixture was steam-distilled to remove all volatile materials, leaving a small amount of brown-black solid. No pure substances could be isolated from this residue.

3-Nitro-4-bromoacetophenone. To 17 g. (0.11 mole) of p-bromoacetophenone was added 140 g. of concentrated sulfuric acid and the mixture was cooled to -5°. To the well-stirred mixture was added dropwise

---

*The writer wishes to thank Mr. J. D. Draper for this analysis.

an ice-cold mixture of 4.9 cc. of fuming nitric acid and 14 cc. of concentrated sulfuric acid. The mixture was allowed to warm to room temperature and was stirred for two and a half hours. The mixture was then poured into 525 cc. of ice water, the crystals filtered off, and washed with water, yielding 14.8 g. of tan crystals (57 percent of the theoretical amount). The product was crystallized from methanol, yielding tan crystals, m.p. 113-115°.

2-Nitro-4-acetyl-4'-methoxydiphenylamine (XXXVIII). In a 200-cc. two-necked glass-jointed flask fitted with a reflux condenser and mercury-sealed stirrer, were placed 6.9 g. (0.03 mole) of 3-nitro-4-bromoacetophenone, 48.4 g. (0.4 mole) of p-anisidine, and 2.5 g. (0.03 mole) of fused sodium acetate. The mixture was stirred and heated at 150° for six hours. The resulting brown-black mixture was cooled and an equal volume of ethanol was added and then an excess of 10 percent acetic acid was added. An oil settled to the bottom and the upper layer was decanted. The black oil was triturated with a little cold ethanol and was then crystallized from hot ethanol, yielding dark brown crystals. The product was recrystallized from ethanol, yielding dark brown crystals, m.p. 194-197°. The compound was repeatedly recrystallized from ethanol, yielding chocolate brown crystals, m.p. 198-199°.

Analysis:* Calc'd for $C_{15}H_{14}O_4N_2$: C, 62.93; H, 4.93

Found: C, 63.04; H, 5.01

C, 63.52; H, 4.85

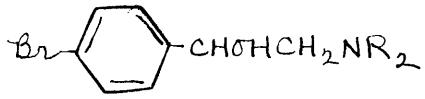
---

*The writer wishes to thank Mr. J. D. Draper for this analysis.

PART III. ETHANOLAMINE DERIVATIVES

Discussion

It has been found that certain compounds containing the ethanolamine side-chain are antimalarial agents. The active compounds of this type are the cinchona alkaloids and certain 4-quinolyl carbinols (Table 26). It was thought that the ethanolamine side-chain, in conjunction with some simple nucleus, might produce active compounds. In view of the desirability, expressed in Part II of this paper, to prepare ethanolamine derivatives of diphenylamine, the synthesis of α-(p-bromophenyl)-β-dialkylaminoethanols (XXXIX) was undertaken. These compounds not only would serve as intermediates in the preparation of diphenylamines



XXXIX

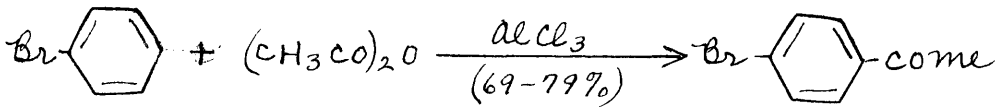
by reacting with aryl amines, but also would serve as representatives of simple ethanolamine derivatives to be tested for antimalarial activity.

The synthesis of α-aryl-β-dialkylaminoethanol derivatives involves first the preparation of a methyl aryl ketone. The ketone is then brominated to produce a bromomethyl aryl ketone which, when reacted with a secondary amine, is converted to a dialkylaminomethyl aryl ketone. The keto group is then reduced to a secondary alcohol by means of catalytic hydrogenation.

$$ArCOMe \xrightarrow{Br_2} ArCOCH_2Br \xrightarrow{R_2NH} ArCOCH_2NR_2 \xrightarrow{(H)} ArCHOHCH_2NR_2$$

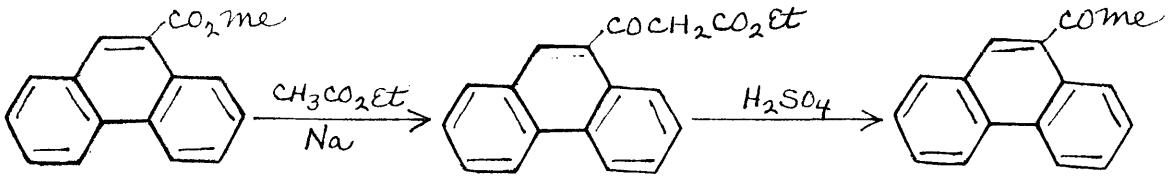
Aryl methyl ketones can be made by utilizing the Friedel and Crafts reaction with acetyl chloride or acetic anhydride.

"Organic Syntheses" (?99):



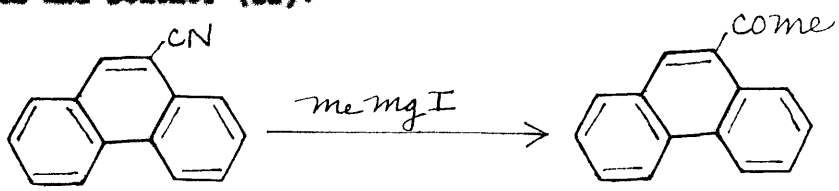
The acetoacetic ester condensation can be used to produce an acylacetic ester which, on hydrolysis and decarboxylation, yields a methyl ketone.

Nosetti and van de Kamp (285):



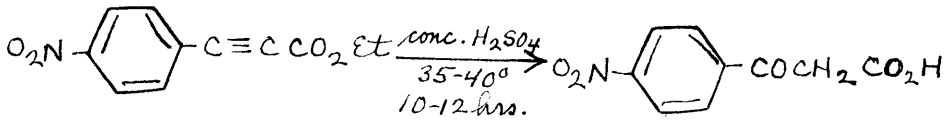
The reaction of a methyl Grignard reagent with a nitrile produces a methyl ketone.

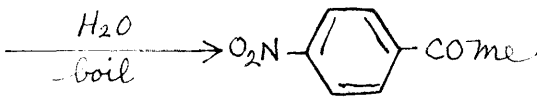
Baehmann and Beatner (11):



An ester of a propiolic acid has been converted to a methyl ketone.

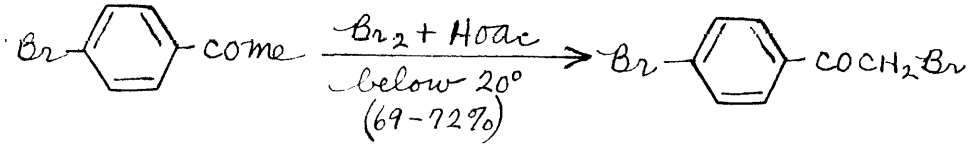
Perkin and Bellenot (910):



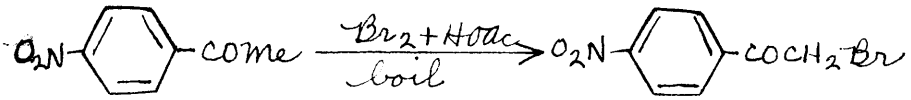


The bromomethyl ketone is prepared by brominating the methyl ketone.

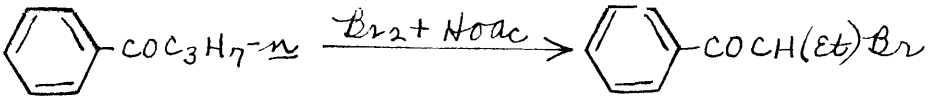
"Organic Syntheses" (901):



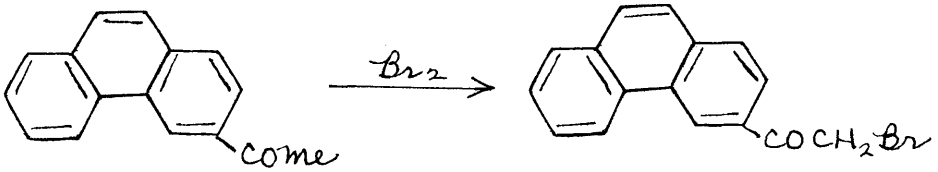
Engler and Zielke (103):



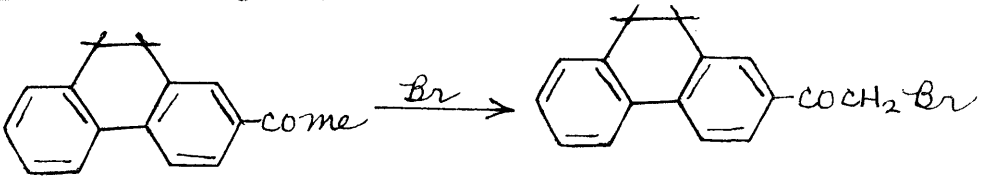
Hyde, Browning and Adams (156):



Mosettig and van de Kamp (286):



Burger and Mosettig (52):



By utilising the Nierenstein reaction (74,243) the bromomethyl ketone can be prepared from an aroyl halide.

King and York (209):

$$ArCOCl \xrightarrow{CH_2N_2} ArCOCHN_2 \xrightarrow{HBr} ArCOCH_2Br$$

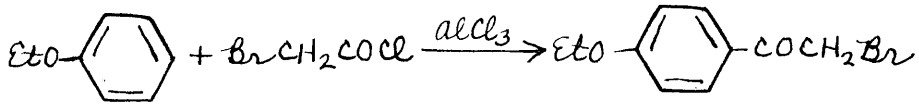
A bromomethyl ketone can be prepared by bromination, hydrolysis, and decarboxylation of an aroylacetic ester.

Rabe, Pasternack and Kindler (323):

$$ArCOCH_2CO_2Et \xrightarrow{Br_2} ArCOCHBrCO_2Et \xrightarrow[boil]{24\%\ HBr} ArCOCH_2Br$$

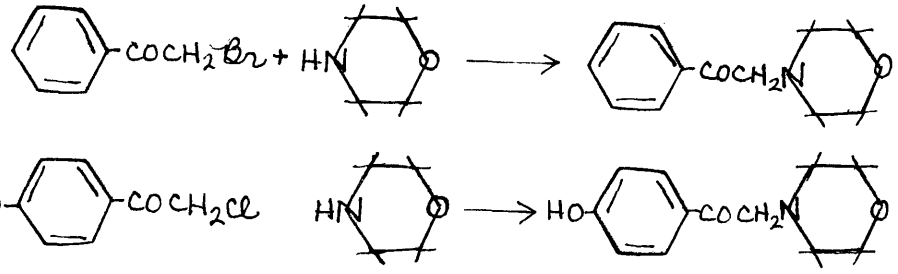
The Friedel and Crafts reaction can be used to prepare a bromomethyl ketone by using an α-haloacyl halide.

Ku and Soboven (223):

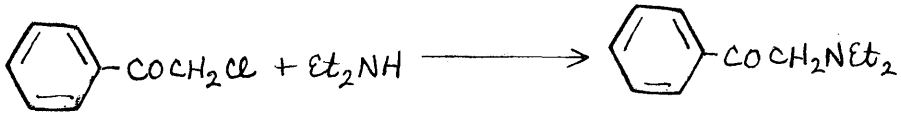


Reaction of the halomethyl ketone with a secondary amine in benzene, ethanol, or ether, produces a dialkylaminomethyl ketone.

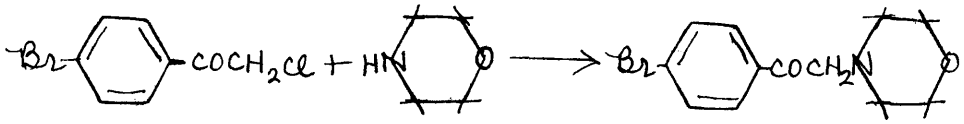
Rubin and Day (335):



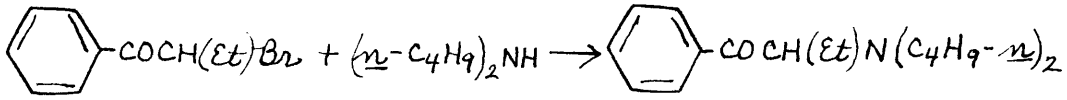
Marvel and du Vigneaud (257):



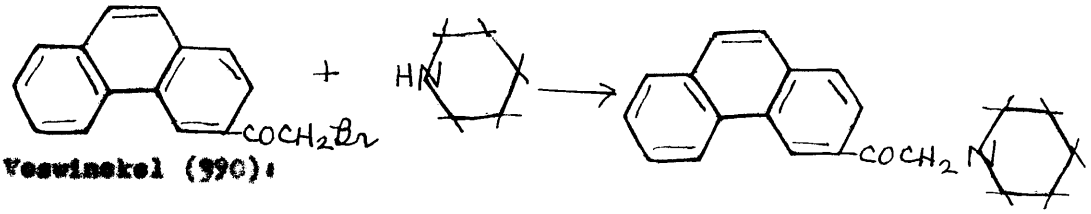
Mason and Ross (259):



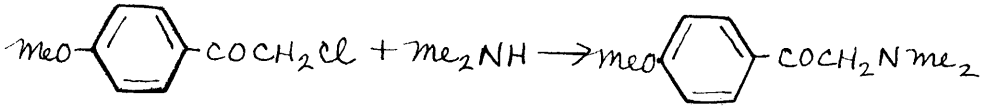
Hyde, Browning and Adams (156):



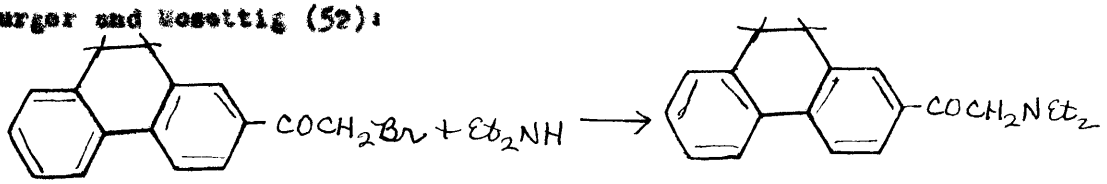
Mosettig and van de Kamp (266):



Veswinekel (390):

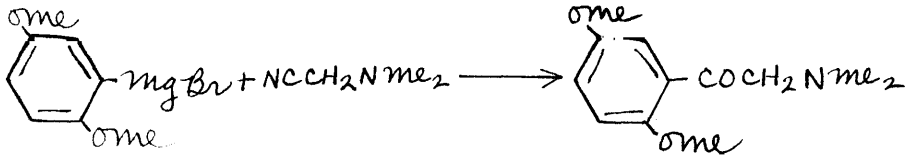


Burger and Mosettig (52):



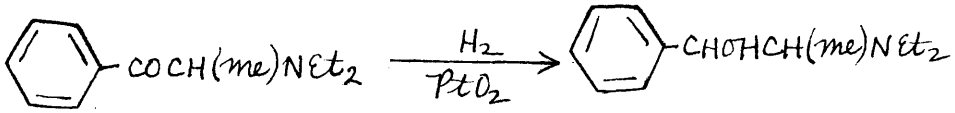
Reaction of an aryl magnesium halide with a dialkylamino-acetonitrile has been used to produce the dialkylaminomethylketone.

Baltzly and Buck (15):

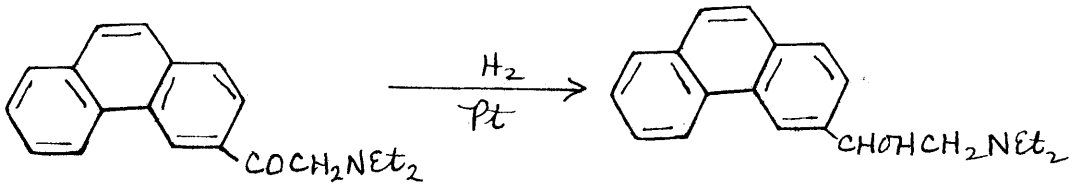


The aminoketone is reduced to the aminoalcohol by means of hydrogen and a catalyst.

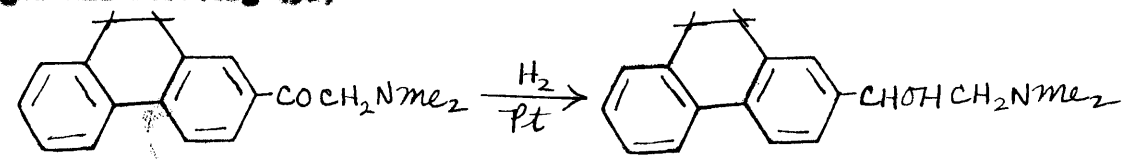
Hyde, Browning and Adams (156):



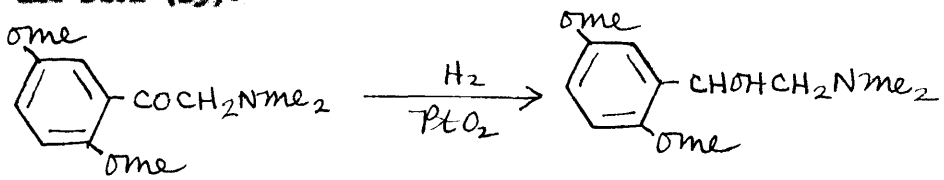
Mosettig and van de Kamp (286):



Burger and Mosettig (52):



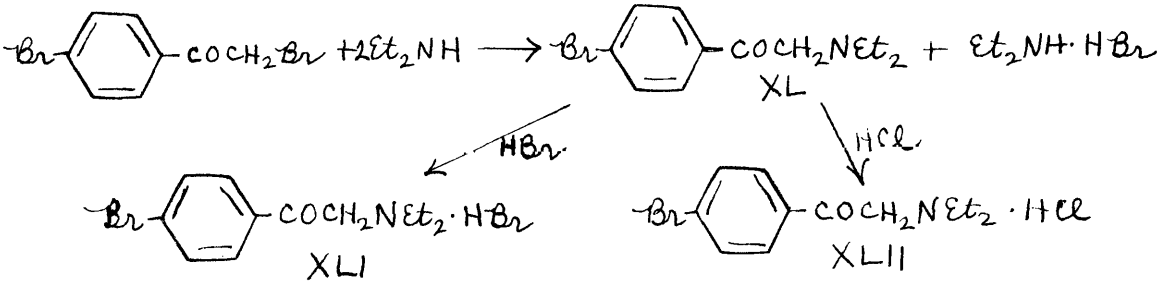
Baltzly and Buck (15):



The ω-dialkylamino-p-bromoacetophenones were prepared by treating a dry benzene or dry benzene-ether solution of one mole of p-bromophenacyl bromide with two moles of secondary amine. The volume of solvent used was the minimum amount to dissolve the p-bromophenacyl bromide at 0°. The heat of reaction was removed by cooling with ice and

the secondary amine hydrobromide started to precipitate almost immediately. The reaction mixture was allowed to stand, preferably in a refrigerator, until the precipitation of secondary amine hydrobromide was complete. In some cases the addition of ether was necessary to cause complete precipitation of the salt. The precipitated salt was removed by filtration. In some cases the filtrate deposited more of the secondary amine hydrobromide and a second filtration was necessary. The filtrate was treated with dry hydrogen bromide or hydrogen chloride to precipitate the hydrohalide salt of the amine ketone. The addition of dry ether at this point caused more complete precipitation of the salt, and if the salt separated as an oil crystallization was induced by adding the ether.

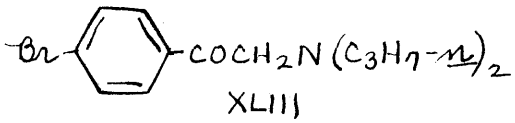
In six preparations of ω-diethylamino-p-bromoacetophenone (XL), the yields of the byproduct diethylamine hydrobromide after reaction times of from two to five hours were 92-98 percent of the theoretical amount, and the yields of crude amine ketone salts were 96-100 percent of the theoretical amount. Both the hydrobromide (XLI) and hydrochloride (XLII) salts of ω-diethylamino-p-bromoacetophenone were prepared. ω-Diethylamino-p-bromoacetophenone hydrochloride (XLII) was also pre-



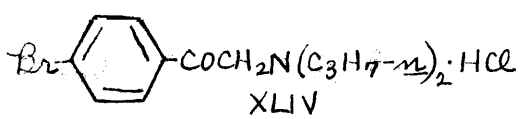
pared by liberating the free base from the hydrobromide salt and treating with dry hydrogen chloride.

In five preparations of ω-di-n-propylamino-p-bromoacetophenone (XLIII) the yields of di-n-propylamine hydrobromide were 88-97 percent

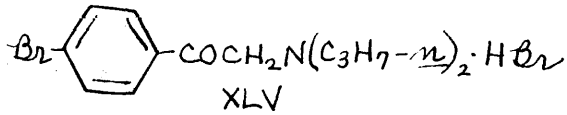
after reaction times of three to twenty-four hours. The hydrochloride salt (XLIV) of the amino ketone was obtained in 95 percent yield, and the hydrobromide salt (XLV) was obtained in 90 percent yield.



XLIII

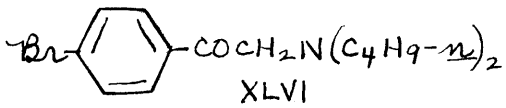


XLIV

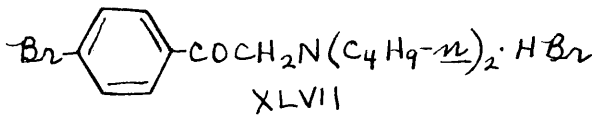


XLV

Five preparations of ω-di-n-butylamino-p-bromoacetophenone (XLVI) gave 87-99 percent yields of di-n-butylamine hydrobromide after reaction times of three to twenty-four hours. ω-Di-n-butylamino-p-bromoacetophenone hydrobromide (XLVII) was obtained in 86.6 percent yield.

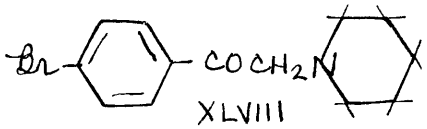


XLVI

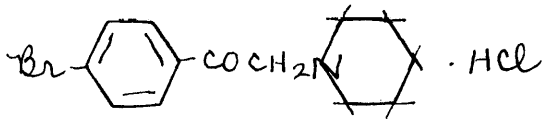


XLVII

In two preparations of ω-piperidyl-p-bromoacetophenone (XLVIII) the yields of piperidine hydrobromide after fifteen and twenty-four hours were 100 percent of the theoretical amount. ω-Piperidyl-p-bromoacetophenone hydrochloride (XLIX) was obtained in 100 percent yield.



XLVIII



XLIX

The p-bromophenacyl bromide used in the preparation of the amino ketones was prepared according to the directions of "Organic Syntheses" (301).

Attempts were made to reduce the amino ketone salts to the amino alcohol salts by shaking with hydrogen and Adams' platinic oxide catalyst, prepared according to the directions of Organic Syntheses" (304), under about 45 pounds pressure. When ω-diethylamino-p-bromoacetophenone hydrobromide was so treated either in 95 percent or absolute ethanol, and even though the theoretical amounts of hydrogen were absorbed, the only product isolated was unchanged amino ketone hydrobromide. When the reduction was run in water solution, nearly three times the theoretical amount of hydrogen was absorbed, and no product could be isolated by crystallization.

Three reductions were run on ω-diethylamino-p-bromoacetophenone hydrochloride in 95 percent ethanol, and in each case the theoretical amount of hydrogen was absorbed. The crystalline products of these reductions were found to be difficult to purify to constant melting point, behaving as mixtures. However, a product was obtained which melted fairly sharply. The carbon and hydrogen analyses were not in agreement with that calculated for the amino alcohol hydrochloride. This product was treated with potassium carbonate to liberate the free base, and the hydrochloride salt was prepared and was found to be identical with ω-diethylamino-p-bromoacetophenone hydrochloride. The aqueous solution from the preparation of the free base was found to contain bromide ions. Hence it is apparent that during the catalytic reduction of the amino ketone hydrochloride reductive removal of the p-bromo group on some of the molecules occurred, with the formation of hydrogen bromide, and the

unreduced ω-diethylamino-p-bromoacetophenone was recovered as a mixture of the hydrobromide and hydrochloride salts. This is substantiated by the fact that the carbon and hydrogen analyses were between those calculated for the hydrobromide and hydrochloride salts of the amino ketone.

A similar reduction of ω-di-n-propylamino-p-bromoacetophenone hydrochloride gave a product which was difficult to purify to constant melting point. It proved to be a mixture of the hydrobromide and hydrochloride salts of the original amino ketone.

When ω-di-n-butylamino-p-bromoacetophenone hydrobromide was subjected to catalytic reduction, only recovered starting product was obtained.

Catalytic reduction of ω-piperidyl-p-bromoacetophenone hydrochloride produced a product which gave carbon and hydrogen analyses between those calculated for the amino ketone hydrobromide and hydrochloride and for the amino alcohol hydrobromide and hydrochloride. It is obvious that this product is a mixture.

It was evident that catalytic reduction could not be used on compounds of this type in which a bromine atom is substituted in the para position. The Meerwein-Ponndorf reduction (268,312), using aluminum isopropoxide, is a specific method for reducing a carbonyl group to an alcohol in excellent yield. Thus, tribromoacetaldehyde is reduced to tribromoethanol:

$$CBr_3CHO \xrightarrow{Al(OCHMe_2)_3} CBr_3CH_2OH$$

Young, Hartung and Crossley (409):

$$CH_3CH{=}CHCHO \xrightarrow[(85\text{-}95\%)]{Al(OCHMe_2)_3} CH_3CH{=}CHCH_2OH$$

Lund (291):

$$C_6H_5COMe \xrightarrow[(93\%)]{Al(OCHME_2)_3} C_6H_5CHOHMe$$

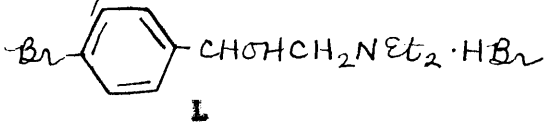
$$C_6H_5CCC_6H_5 \xrightarrow{Al(OCHMe_2)_3} C_6H_5CHOHC_6H_5$$

The reduction is an equilibrium (111) which is displaced in the direction to form the alcohol by distillation of the acetone formed.

$$3\ \begin{matrix}R_1\\R_2\end{matrix}\!\!>\!C{=}O + Al(OCHMe_2)_3 \rightleftharpoons \left(\begin{matrix}R_1\\R_2\end{matrix}\!\!>\!CHO\right)_3 Al + 3\ O{=}CMe_2$$

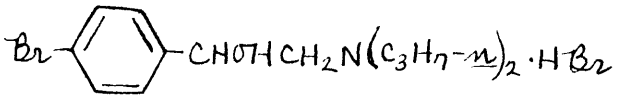
In general, the reductions of the amino ketones were carried out by fractionally distilling a benzene solution of the freshly prepared amino ketone with a one-half mole excess of aluminum isopropoxide, prepared according to Young, Hartung and Crossley (409), adding dry isopropanol, and distilling again until the distillate no longer gave a test for acetone. All the solvent was removed by vacuum distillation and the residue was decomposed with cold hydrochloric acid. The aqueous solution of the hydrochloride of the amino alcohol was then made strongly alkaline so as to liberate the amino alcohol as the free base and keep the aluminum in solution as the aluminate ion. The amino alcohol was extracted with benzene, the benzene solution was dried, and the hydrobromide precipitated by treatment with hydrogen bromide. The amino alcohol hydrobromide was purified by crystallization from ethanol-ether.

α-(p-Bromophenyl)-β-diethylaminoethanol hydrobromide (L)



L

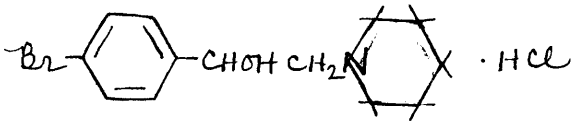
was prepared in this way in 70 percent yield. In the case of the reduction of ω-di-n-propylamino-p-bromoacetophenone, decomposition of the reaction product with hydrochloric acid produced a small amount of dark red oil which was extracted from the aqueous solution with ether. α-(p-Bromophenyl)-β-di-n-propylaminoethanol hydrobromide (LI) was obtained in 70 percent yield. A second reduction of ω-di-n-propyl-



LI

amino-p-bromoacetophenone was varied by treating the acidified reduction product with a large amount of hot water, and removing the small amount of dark red gummy impurity by filtration.

The reduction of ω-piperidyl-p-bromoacetophenone was carried out as described above and after acidification the reduction product was treated with a large volume of hot water and filtered from a small amount of gummy impurity. α-(p-Bromophenyl)-β-piperidylethanol hydrochloride (LII) was obtained in 81.2 percent yield.

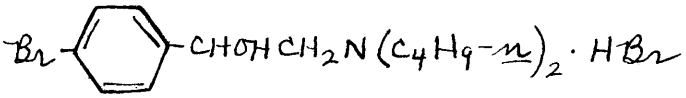


LII

In two reductions of ω-di-n-butylamino-p-bromoacetophenone the dark colored oil which was obtained after acidification of the reduction product accounted for most of the product, and little or no reduction product was obtained. It was thought that the decomposition was the result of excessive heating during the reduction and so the reaction was repeated under reduced pressure so that only moderate heating was necessary, but again the acid-insoluble oil was obtained in large quantity.

It was observed that during the reduction of the amino ketones as free bases as described above, considerable darkening of the reaction mixture occurred. This darkening is probably the result of decomposition and probably gives rise to the acid-insoluble oils which were formed in small amounts in the cases of the di-n-propylamino and piperidyl compounds, and in large amounts in the case of the di-n-butylamino compound.

Apparently the di-n-butylamino compound is very sensitive to the action of aluminum isopropoxide and is almost entirely decomposed by it. The reduction was carried out on ω-di-n-butylamino-p-bromoacetophenone hydrobromide, using a one and a half mole excess of aluminum isopropoxide, and the reaction mixture remained entirely colorless and no oily decomposition product was obtained. α-(p-Bromophenyl)-β-di-n-butylaminoethanol hydrobromide (LIII) was obtained in 93 percent yield by this procedure.



LIII

Compounds L, LI, LII, and LIII were submitted for pharmacological testing.

Experimental

p-Bromophenacyl Bromide. In a 500-cc. Erlenmeyer flask was placed 79 g. (0.35 mole) of p-bromoacetophenone and 145 cc. of glacial acetic acid. To the resulting solution was very slowly added 53 g. (0.35 mole) of bromine, keeping the temperature below 20°. The mixture was vigorously shaken by hand during the addition which took forty-five minutes. The flask was then cooled in ice and the product removed by filtration. The crude crystals were washed with cold 50 percent ethanol until colorless. The product was crystallized from 580 cc. of hot ethanol, yielding colorless needles, wt. 79 g., (81 percent of the theoretical amount).

The acetic acid mother liquor was treated with water until turbid and then chilled, yielding yellow crystals. The alcohol mother liquor, on treatment with water, yielded a further crop of crystals. The product recovered from both liquors weighed 5 g.

ω-Diethylamino-p-bromoacetophenone Hydrobromide (XLI). To a solution of 13.9 g. (0.05 mole) of p-bromophenacyl bromide in 150 cc. of dry benzene in a 200-cc. flask was added 7.3 g., 10.3 cc., (0.1 mole) of diethylamine. The flask was stoppered and shaken and the heat of reaction removed by cooling the flask in ice. A crystalline precipitate of diethylamine hydrobromide formed almost immediately and the benzene solution became yellow. The reaction mixture was allowed to stand. After two hours the diethylamine hydrobromide was removed by filtration and washed with several small portions of dry benzene until the crystals were colorless. The washings were added to the main filtrate. Care was exercised to keep the benzene filtrate dry. The yield of diethylamine hydrobromide was 7.0 g. After standing for thirty minutes the filtrate

had deposited a further quantity of precipitate and the filtration and washing processes were repeated. The total yield of diethylamine hydrobromide was 7.4 g. (96 percent of the theoretical amount). A similar run, with the same time of standing, yielded 7.5 g. (98 percent of the theoretical amount) of diethylamine hydrobromide. Two more runs were made on the same quantities of starting products but in which the reaction time was three hours, and the yields of diethylamine hydrobromide were 7.2 g. (94 percent of the theoretical amount) in each case. A run in which 41.7 g. (0.15 mole) of p-bromophenacyl bromide was used, with reaction time of three hours, produced 22.0 g. (95 percent of the theoretical amount) of diethylamine hydrobromide.

The benzene filtrate was cooled and saturated with dry hydrogen bromide and a pale yellow crystalline precipitate formed. The crystals were removed by filtration and washed with dry benzene. The yields of ω-diethylamino-p-bromoacetophenone hydrobromide from the 0.05 mole runs were 17.0-17.5 g. (97-100 percent of the theoretical amount). The 0.15 mole run gave 59.6 g. (100 percent of the theoretical amount) of the hydrobromide. The ω-diethylamino-p-bromoacetophenone hydrobromide was crystallized several times from absolute ethanol or absolute ethanol-ether to give colorless crystals, m.p. 199.1-199.8°.

Analysis: Calc'd for $C_{12}H_{17}ONBr_2$: C, 41.05; H, 4.88

Found*: C, 41.57; H, 4.88

Volhard titration of ionizable halogen:

Calc'd for $C_{12}H_{17}ONBr_2$: Br, 22.76

Found: Br, 22.6

---

*The writer wishes to thank Columbia University for this analysis.

ω-Diethylamino-p-bromoacetophenone Hydrochloride (XLII).

To a solution of 41.7 g. (0.15 mole) of p-bromophenacyl bromide in 450 cc. of dry benzene in a 1-l. flask was added 21.9 g., 30.9 cc., (0.3 mole) of diethylamine. The flask was stoppered, shaken, and cooled with ice to remove the heat of reaction. A colorless precipitate formed. The suspension was allowed to stand four hours at room temperature and one hour in the refrigerator, and then the diethylamine hydrobromide was removed by filtration. The precipitate was washed with dry ether and the filtrates were combined. The yield of colorless diethylamine hydrobromide was 21.4 g. (99 percent of the theoretical amount).

The yellow benzene-ether solution was cooled in an ice bath and saturated with dry hydrogen chloride, yielding 39.1 g. of nearly colorless crystals of ω-diethylamino-p-bromoacetophenone hydrochloride. The addition of dry ether caused the precipitation of a further 5.9 g. of the hydrochloride. The total yeild was 44.9 g. (96 percent of the theoretical amount).

ω-Diethylamino-p-bromoacetophenone hydrochloride was also prepared from the hydrobromide (XLI). A solution of 21.1 g. (0.06 mole) of ω-diethylamino-p-bromoacetophenone hydrobromide in 100 cc. of water was made alkaline by adding a solution of 10 g. of potassium carbonate in 50 cc. of water, causing the separation of ω-diethylamino-p-bromoacetophenone as a yellow oil. The free base was extracted with ether, and the ether extract was dried over Drierite, and saturated with dry hydrogen chloride. A pale yellow semi-solid precipitate formed. The ether was decanted from the precipitate and the flask was placed in an evacuated desiccator over phosphorous pentoxide for twelve hours. The dry hydrochloride was crystallized from absolute ethanol-ether, yielding 17.7 g. (97 percent of the theoretical amount) of colorless crystals.

The ω-diethylamino-p-bromoacetophenone hydrochloride was crystallized from absolute ethanol-ether to a constant melting point of 177.6-179.6° (sinters 171.7°).

Analysis: Calc'd for $C_{12}H_{17}ONBrCl$: C, 47.00; H, 5.59

Found*: C, 46.51; H, 5.69

Volhard titration of ionizable halogen:

Calc'd for $C_{12}H_{17}ONBrCl$: Cl, 11.56

Found: Cl, 11.5

ω-Di-n-propylamino-p-bromoacetophenone Hydrochloride (XLIV).

To a solution of 13.9 g. (0.05 mole) of p-bromophenacyl bromide in 125 cc. of dry benzene in a 200-cc. flask was added 10.1 g., 13.7 cc., (0.1 mole) of di-n-propylamine. The flask was stoppered, shaken, and cooled in an ice bath to remove the heat of reaction. A crystalline precipitate of di-n-propylamine hydrobromide formed immediately. After standing for three hours the precipitate was removed by filtration and washed with a small amount of dry ether. The yield of colorless di-n-propylamine hydrobromide was 8.2 g. (90 percent of the theoretical amount).

When this reaction was run on a solution of 27.8 g. (0.1 mole) of p-bromophenacyl bromide in 600 cc. of dry ether and 100 cc. of dry benzene the precipitation of di-n-propylamine hydrobromide was slow. After three hours 13.5 g. was obtained, after a further seven hours 2.5 g. more was obtained, and after a further fourteen hours 0.9 g. more was obtained. The total yield was 16.9 g. (93 percent of the theoretical amount).

---

*The writer wishes to thank the National Institute of Health for this analysis.

The yellow filtrate from the 0.05 mole run was cooled by means of an ice bath and saturated with dry hydrogen chloride, yielding a deep green solution. The solution was distilled to half the original volume, cooled, and treated with dry ether, causing a crystalline precipitate to form. The light gray precipitate of ω-di-n-propylamino-p-bromoacetophenone hydrochloride weighed 16.7 g. (95 percent of the theoretical amount). The product was repeatedly crystallized from absolute ethanol-ether, yielding colorless crystals, m.p. 171.7-172.6° (sinters 170.7°).

Analysis: Calc'd for $C_{14}H_{21}ONBrCl$: C, 50.24; H, 6.32

Found: C, 49.11; H, 6.08

C, 49.73; H, 6.26

* C, 49.27; H, 6.03

Volhard titration of ionizable halogen:

Calc'd for $C_{14}H_{21}ONBrCl$: Cl, 10.59

Found: Cl, 10.4

ω-Di-n-propylamino-p-bromoacetophenone Hydrobromide (XLV). To a solution of 13.9 g. (0.05 mole) of p-bromophenacyl bromide in 150 cc. of dry benzene in a 500-cc. flask was added 10.1 g., 13.7 cc. (0.1 mole) of di-n-propylamine. The flask was stoppered, shaken, and cooled by means of an ice bath for one hour. To the suspension was added 350 cc. of dry ether, and after cooling in an ice bath the crystalline di-n-propylamine hydrobromide was removed by filtration, wt. 7.0 g. After seventeen hours more in the refrigerator a further yield of 1.0 g. was obtained. The total yield of di-n-propylamine hydrobromide was 8.0 g.

---

*The writer wishes to thank Mr. J. D. Draper for this analysis.

(88 percent of the theoretical amount).

The yellow benzene-ether filtrate was concentrated on the steam bath to 200 cc., and after cooling with an ice bath the solution was saturated with dry hydrogen bromide. A pale green crystalline precipitate formed. After adding 300 cc. of dry ether the ω-di-n-propylamino-p-bromoacetophenone hydrobromide was removed by filtration, wt. 17.1 g. (90 percent of the theoretical amount). Crystallization from absolute ethanol-ether yielded colorless crystals with a constant melting point of 184.2-184.8°.

Analysis: Calc'd for $C_{14}H_{21}ONBr_2$: C, 44.35; H, 5.59

Found*: C, 44.46; H, 5.38

" C, 44.60; H, 5.86

" C, 44.70; H, 5.54

Volhard titration of ionizable halogen:

Calc'd for $C_{14}H_{21}ONBr_2$: Br, 21.09

Found: Br, 21.3

ω-Di-n-butylamino-p-bromoacetophenone Hydrobromide (XLVII).

To a solution of 27.8 g. (0.1 mole) of p-bromophenacyl bromide in 150 cc. of dry ether and 200 cc. of dry benzene in a 500-cc. flask was added 25.8 g. (0.2 mole) of di-n-butylamine. The flask was stoppered, shaken, and cooled by means of an ice bath. Within one minute a crystalline precipitate of di-n-butylamine hydrobromide formed. After three hours the precipitate was removed by filtration and washed with a little dry ether, the washings being added to the first filtrate. The yield of colorless di-n-butylamine hydrobromide was 18.3 g. (87 percent of the

---

*The writer wishes to thank Mr. J. D. Draper for this analysis.

theoretical yield).

The yellow filtrate was cooled with an ice bath and saturated with dry hydrogen bromide, causing the precipitation of nearly colorless crystals of ω-di-n-butylamino-p-bromoacetophenone hydrobromide. The crystals were removed by filtration and from the filtrate a further crop of 4.0 g. of colorless crystals was obtained by adding dry ether. The total yield was 35.3 g. (86.6 percent of the theoretical amount). The product was crystallized to constant melting point, yielding colorless crystals from absolute ethanol-ether. The compound exhibits a transition point at 145-146°, partially melting. At 148-149° it has completely resolidified. It melts completely at 176.5-177.5°.

Analysis: Calc'd for $C_{18}H_{29}ONBr_2$: C, 47.19; H, 6.19

Found: C, 47.23; H, 6.21

C, 47.17; H, 6.06

Volhard titration of ionizable halogen:

Calc'd for $C_{18}H_{29}ONBr_2$: Br, 19.62

Found: Br, 19.7

When 19.9 g. (0.05 mole) of p-bromophenacyl bromide was dissolved in 150 cc. of benzene and reacted with di-n-butylamine for twenty-four hours, 8.2 g. of di-n-butylamine hydrobromide was obtained. All the benzene was distilled from the filtrate and after the residue was treated with 50 cc. of dry ether 2.2 g. more of di-n-butylamine hydrobromide was obtained. The total yield was 10.4 g. (99 percent of the theoretical amount).

ω-Piperidyl-p-bromoacetophenone Hydrochloride (XLIX). To a solution of 27.8 g. (0.1 mole) of p-bromophenacyl bromide in 250 cc. of dry benzene in a 500-cc. flask was added 17.0 g., 19.7 cc. (0.2 mole) of freshly distilled piperidine. The flask was stoppered, shaken, and cooled

by means of an ice bath to remove the heat of reaction. The flask was allowed to stand in the refrigerator for fifteen hours. The precipitated piperidine hydrobromide was removed by filtration and washed with several small portions of dry ether until colorless. The yield of piperidine hydrobromide was 16.6 g. (100 percent of the theoretical amount).

The yellow filtrate, combined with the ether washings, was cooled with an ice bath and saturated with dry hydrogen chloride. The cream-colored precipitate of ω-piperidyl-p-bromoacetophenone hydrochloride was removed by filtration, wt. 31.8 g. (100 percent of the theoretical amount). The compound was crystallized from absolute ethanol to constant melting point, yielding colorless crystals, m.p. on slow heating 224.7-225.7°, on rapid heating 230.5-231.5°.

Analysis: Calc'd for $C_{13}H_{17}ONBrCl$: C, 49.00; H, 5.38

Found*: C, 48.96; H, 5.05

\+ C, 48.79; H, 5.13

Volhard titration of ionizable halogen:

Calc'd for $C_{13}H_{17}ONBrCl$: Cl, 11.13

Found: Cl, 10.9

Adams' Platinic Oxide Catalyst. In a porcelain dish was prepared a solution of 3.5 g. of chloroplatinic acid hexahydrate in 10 cc. of water, and to this was added 35 g. of C.P. sodium nitrate. The mixture was evaporated to dryness by heating gently over a flame while stirring with a thermometer. The temperature was then raised, 350-370° being reached within about ten minutes. Fusion took place, brown oxides of nitrogen were evolved, and a precipitate of brown platinic oxide gradually

---

*The writer wishes to thank Mr. J. D. Draper for this analysis.

separated. By the end of fifteen minutes, when the temperature had reached about 400°, the evolution of gas had greatly decreased. At the end of twenty minutes the temperature was 550°. At this point the vigorous evolution of oxides of nitrogen had ceased, and a gentle evolution of gas took place. The temperature was held at 550-560° until thirty minutes had elapsed, when the fusion was complete.

The mass was allowed to cool and was treated with 50 cc. of water. The brown precipitate was centrifuged and washed with water until practically free from nitrates. The catalyst was then sucked dry on a Hirsch funnel fitted with a hardened filter paper. The oxide was dried in a desiccator over phosphorous pentoxide.

Catalytic Reduction of ω-Diethylamino-p-bromoacetophenone Hydrobromide. A. A solution of 10.5 g. (0.09 mole) of ω-diethylamino-p-bromoacetophenone hydrobromide in 125 cc. of absolute ethanol was shaken with 0.1 g. of Adams' platinic oxide catalyst under 49.8 lbs. pressure of hydrogen for seventy-five minutes, and 0.035 mole of hydrogen was absorbed. The solution was filtered from the catalyst and concentrated in vacuo. The residual liquid was cooled in ice, yielding 8.9 g. of colorless crystals, m.p. 187-190°. This product was recovered ω-diethylamino-p-bromoacetophenone hydrobromide since it did not depress the melting point of an authentic sample of ω-diethylamino-p-bromoacetophenone hydrobromide. The mother liquor, when treated with ether, yielded 1.6 g. more of starting product. The total recovery was 9.9 g. (94 percent).

B. A solution of 21.0 g. (0.06 mole) of ω-diethylamino-p-bromoacetophenone hydrobromide in 150 cc. of 95 percent ethanol was shaken with 0.2 g. of Adams' platinic oxide catalyst under 35.3 lbs. pressure of hydrogen for forty-four minutes, and 0.06 mole of hydrogen was absorbed.

After removing the catalyst the solution was concentrated and colorless crystals were obtained. After several crystallizations from absolute ethanol the product had a melting point of 193.0-193.5° and did not depress the melting point of a sample of ω-diethylamino-p-bromoacetophenone hydrobromide.

The mother liquor was concentrated further and yielded a pink crystalline product, m.p. 157-174°. Several crystallizations from absolute ethanol brought the melting point to 191.0-192.1°.

The combined mother liquors were concentrated to a small volume and diluted with a large volume of dry acetone, but no crystals formed. The solution was concentrated and the residual viscous liquid was dissolved in 30 cc. of water, and made alkaline with a solution of 4 g. of potassium carbonate in 70 cc. of water, causing a tan oil to separate. The free amine was extracted with ether and the yellow ether solution was dried over anhydrous potassium carbonate and Drierite. The solution was saturated with dry hydrogen chloride and a greenish oil separated. The ether was decanted from the oil, and all attempts to induce the oil to crystallize failed.

C. A solution of 10.5 g. (0.03 mole) of ω-diethylamino-p-bromoacetophenone hydrobromide in 125 cc. of water was shaken with 0.2 g. of Adams' platinic oxide catalyst under 38.1 lbs. pressure of hydrogen for seventy-five minutes, and 0.033 mole of hydrogen was absorbed. The solution was filtered from the catalyst and concentrated in vacuo, but the residual liquid could not be induced to crystallize.

Catalytic Reduction of ω-Diethylamino-p-bromoacetophenone Hydrochloride, A. A solution of 12.2 g. (0.04 mole) of ω-diethylamino-p-bromoacetophenone hydrochloride in 130 cc. of 95 percent ethanol was shaken with 0.1 g. of Adams' platinic oxide catalyst under 35.0 lbs.

pressure of hydrogen for thirty minutes, and 0.041 mole of hydrogen was absorbed. The pale yellow solution was filtered from the catalyst and concentrated. The residual liquid was treated with a large volume of ether, causing an oil to separate. The ether was decanted, the oil was dissolved in ethanol, and ether was added. The solution deposited 4.9 g. of crystals, m.p. 174-180°. Recrystallization from ethanol-ether yielded 3.6 g. of crystals, m.p. 179-183°. A second recrystallization gave 3.3 g. of crystals, m.p. 183-185°. A third recrystallization gave 3.1 g. of crystals, m.p. 184-185.5°. A fourth recrystallization gave 2.8 g. of colorless plates, m.p. 187-189°.

B. A solution of 9.2 g. (0.03 mole) of ω-diethylamino-p-bromoacetophenone hydrochloride in 50 cc. of 95 percent ethanol was shaken with 0.1 g. of Adams' platinic oxide catalyst under 35.9 lbs. pressure of hydrogen for thirty-eight minutes, and 0.029 mole of hydrogen was absorbed. The catalyst was filtered off, 20 cc. of dry benzene was added, and the solution was distilled to a volume of 30 cc. Dry ether was added and the solution was cooled in the refrigerator, yielding 2.7 g. of colorless crystals, m.p. 176-179°. The mother liquor yielded 1.0 g. of colorless crystals, m.p. 179-182°.

C. A solution of 9.2 g. (0.03 mole) of ω-diethylamino-p-bromoacetophenone hydrochloride in 50 cc. of 95 percent ethanol was shaken with 0.1 g. of Adams' platinic oxide catalyst under 37.7 lbs. pressure of hydrogen for thirty-eight minutes, and 0.029 mole of hydrogen was absorbed. The catalyst was removed by filtration and the filtrate was concentrated on the steam bath. A large volume of ether was added, yielding colorless crystals.

These crystals were combined with those from runs A and B and were crystallized to constant melting point from ethanol-ether, yielding

colorless crystals, m.p. 186.4-187.4° (sinters 185.6°)

Analysis: Calc'd for $C_{12}H_{19}ONBrCl$: C, 46.69; H, 6.20

Found: C, 41.62; H, 4.97

* C, 41.39; H, 4.94

* C, 41.98; H, 4.92

** C, 41.62; H, 5.09

*** C, 42.09; H, 4.66

*** C, 41.60; H, 4.80

It is obvious from these analyses that the compound was not the expected α-(p-bromophenyl)-β-diethylaminoethanol hydrochloride.

A solution of 4.5 g. of the analytical sample of the above compound in 40 cc. of water was made alkaline by adding potassium carbonate solution. The yellow oil which separated was extracted with benzene, the benzene extract was washed with water and dried by refluxing into a moisture-point receiver. The dried benzene solution was saturated with dry hydrogen chloride, causing the separation of a yellow oil which solidified on standing. The hydrochloride was crystallized to a constant melting point of 172.6-173.6°. A mixed melting point with ω-diethylamino-p-bromoacetophenone hydrochloride showed no depression. The aqueous solution from the preparation of the free base was acidified with hydrochloric acid and chlorine water was added. The solution became orange and imparted an orange-red color to carbon tetrachloride. This indicates that the product from the catalytic reduction contains ionizable

---

*The writer wishes to thank Columbia University for this analysis.
**The writer wishes to thank the National Institute of Health for this analysis.
***The writer wishes to thank Mr. J. E. Draper for this analysis.

bromine. Therefore it is a mixture of the hydrochloride and hydrobromide of ω-diethylamino-p-bromoacetophenone.

Catalytic Reduction of ω-Di-n-propylamino-p-bromoacetophenone Hydrochloride. A solution of 13.4 g. (0.04 mole) of ω-di-n-propylamino-p-bromoacetophenone hydrochloride in 100 cc. of 95 percent ethanol was shaken with 0.1 g. of Adams' platinic oxide catalyst under 42.3 lbs. pressure of hydrogen for thirty-eight minutes, and 0.095 mole of hydrogen was absorbed. The solution was filtered from the catalyst and concentrated to a small volume. Benzene was added and the solution again concentrated to a small volume. Ether was added and 6.7 g. of colorless crystals were obtained, m.p. 172.1-176.5°. Five crystallizations from ethanol-ether gave colorless crystals, m.p. 180.6-182.1°.

Analysis: Calc'd for $C_{14}H_{22}ONBrCl$: C, 49.94; H, 6.89

Found*: C, 45.71; H, 5.55

" C, 45.90; H, 5.59

This product is probably a mixture of the hydrobromide and hydrochloride of ω-di-n-propylamino-p-bromoacetophenone, and not the expected α-(p-bromophenyl)-β-di-n-propylaminoethanol hydrochloride.

Catalytic Reduction of ω-Di-n-butylamino-p-bromoacetophenone Hydrobromide. A solution of 20.4 g. (0.05 mole) of ω-di-n-butylamino-p-bromoacetophenone hydrobromide in 70 cc. of 95 percent ethanol was shaken with 0.1 g. of Adams' platinic oxide catalyst under 40.0 lbs. pressure of hydrogen for forty-five minutes, and 0.054 mole of hydrogen was absorbed. The catalyst was removed by filtration, the filtrate was distilled to half the initial volume, 15 cc. of dry benzene was added,

---

*The writer wishes to thank Mr. J. D. Draper for this analysis.

and the solution was distilled to a small volume. The residual liquid was treated with ether, causing an oil to separate. After shaking and scratching the oil crystallized. The colorless crystals were removed by filtration, wt. 9.1 g. The product was crystallized from ethanol-ether yielding colorless crystals, m.p. 174.6-175.6°, lower transition point 145-146°. This product did not depress the melting point of a sample of ω-di-n-butylamino-p-bromoacetophenone hydrobromide, and so is recovered starting material.

Catalytic Reduction of ω-Piperidyl-p-bromoacetophenone Hydrochloride. A solution of 12.7 g. (0.04 mole) of ω-piperidyl-p-bromoacetophenone hydrochloride in 100 cc. of 95 percent ethanol was shaken with 0.2 g. of Adams' platinic oxide catalyst under 42.5 lbs. pressure of hydrogen for thirty minutes, and 0.045 mole of hydrogen was absorbed. The catalyst was removed by filtration and the filtrate was concentrated to 100 cc. On cooling, the solution deposited 5.3 g. of colorless crystals, m.p. 229-240°. The compound crystallized from ethanol-ether to a constant melting point of 242.0-243.0°.

Analysis: Calc'd for $C_{15}H_{19}ONBrCl$: C, 48.69; H, 5.97

Found*: C, 45.58; H, 4.95

* C, 45.10; H, 4.80

Therefore, this product is not the expected α-(p-bromophenyl)-β-piperidylethanol hydrochloride but is probably a mixture of the hydrobromide and hydrochloride of ω-piperidyl-p-bromoacetophenone.

Aluminum Isopropoxide. In a 1-l. glass-jointed flask, fitted with an efficient reflux condenser, were placed 50 g. of aluminum turnings,

---

*The writer wishes to thank Mr. J. D. Draper for this analysis.

600 cc. of isopropanol (distilled from sodium), and 2.5 g. of mercuric chloride. The mixture was refluxed on a steam bath for six hours. The excess isopropanol was distilled off and the aluminum isopropoxide was purified by distillation, b.p. 142-147°/4 mm., yielding 365 g. (96.6 percent of the theoretical amount) of colorless solid.

α-(p-Bromophenyl)-β-diethylaminoethanol Hydrobromide (L). A solution of 17.6 g. (0.05 mole) of ω-diethylamino-p-bromoacetophenone hydrobromide in water was made alkaline with potassium carbonate, and the yellow oil which separated was extracted with benzene. The benzene solution of the ω-diethylamino-p-bromoacetophenone was washed with water and dried by refluxing into a moisture-point receiver, and was then concentrated to 75 cc.

To this benzene solution contained in a 200-cc. two-necked glass-jointed flask, fitted with a dropping funnel and helix-packed fractionating column with controlled takeoff, was added 15.3 g. (0.075 mole) of aluminum isopropoxide. The solution was slowly distilled and the distillate was periodically tested for acetone with 2,4-dinitrophenylhydrazine reagent. The first portions of distillate gave strong positive tests for acetone. After most of the benzene had been distilled dry isopropanol was added to the reaction flask and the distillation continued until the distillate no longer contained acetone.

The bulk of the solvent was removed by distillation at reduced pressure, and the aluminum-complex was decomposed with cold 10 percent hydrochloric acid. The solution was again distilled until all the isopropanol was removed. The residual liquid was diluted with water and made strongly alkaline with cold potassium hydroxide solution. The aluminum hydroxide which precipitated dissolved in the excess potassium

hydroxide and a brown oil separated. The oil was extracted with benzene, the benzene solution was washed with sodium chloride solution, and dried over Drierite. The dry solution was saturated with dry hydrogen bromide causing a brown oil to separate. Dry ether was added, and then absolute ethanol was added until the oil dissolved. When the solution was cooled in the refrigerator an oil separated. The solution was distilled at the water pump until all the solvent was removed, and the residual oil was dissolved in absolute ethanol. The solution was cooled by means of a dry ice-acetone bath and crystals formed. The tan crystals were removed by filtration, wt. 8.1 g. An addition 4.0 g. was obtained from the mother liquor. The total yield of α-(p-bromophenyl)-β-diethylaminoethanol hydrobromide was 12.1 g. (70 percent of the theoretical amount). Three crystallizations from absolute ethanol-ether gave colorless crystals having a constant melting point of 135.0-135.5°.

Analysis: Calc'd for $C_{12}H_{19}ONBr_2$: C, 40.81; H, 5.42

Found*: C, 40.99; H, 5.28

* C, 41.00; H, 5.30

Volhard titration of ionizable halogen:

Calc'd for $C_{12}H_{19}ONBr_2$: Br, 22.63

Found: Br, 22.5

Br, 22.5

α-(p-Bromophenyl)-β-di-n-propylaminoethanol Hydrobromide (LI).

To a solution of 13.9 g. (0.05 mole) of p-bromophenacyl bromide in 150 cc. of dry benzene in a 200-cc. flask was added 10.1 g., 13.7 cc. (0.1 mole) of di-n-propylamine. The flask was stoppered, shaken, and allowed to stand in the refrigerator for eighteen hours. The suspension was then treated with 200 ml. of dry ether and the crystalline di-n-propylamine hydrobromide

---

* The writer wishes to thank Mr. J. D. Draper for this analysis.

was removed by filtration, wt. 3.8 g. (97 percent of the theoretical amount). The filtrate was concentrated to 100 cc.

To this solution in a 200-cc. two-necked glass-jointed flask fitted with a dropping funnel and helix-packed fractionating column with controlled take-off, was added 15.9 g. (0.075 mole) of aluminum isopropoxide, and the resulting solution was slowly distilled. After most of the benzene was stilled, 100 cc. of dry isopropanol was added through the dropping funnel and the distillation was continued until the distillate gave a negative test with 2,4-dinitrophenylhydrazine reagent. The solution was then distilled in vacuo to remove all the solvent, leaving a red semi-crystalline mass. The residue was thoroughly chilled in ice and acidified with 100 cc. of ice-cold 10 percent hydrochloric acid to decompose the aluminum complex. A small amount of dark red oil remained undissolved, and was removed by extraction with ether. The reddish aqueous solution was chilled and made strongly alkaline with ice-cold potassium hydroxide solution. The aluminum hydroxide which precipitated at first dissolved in the excess alkali and a brown oil separated. The oil was extracted with five 50-cc. portions of benzene and the benzene extract was washed with two 50-cc. portions of water. The benzene extract was dried by distilling into a moisture-point receiver, and the dried solution was cooled by means of an ice bath and saturated with dry hydrogen bromide, yielding tan crystals. The salt was removed by filtration and one crystallization from absolute ethanol-ether yielded 19.4 g. (70 percent of the theoretical amount) of α-(p-bromophenyl)-β-di-n-propylaminoethanol hydrobromide. The product was crystallized to constant melting point from absolute ethanol-ether, yielding colorless crystals, m.p. 138.9-139.3°.

Analysis: Calc'd for $C_{14}H_{22}ONBr_2$: C, 44.11; H, 6.08

Found*: C, 44.15; H, 5.85

" C, 44.20; H, 5.96

Volhard titration of ionizable halogen:

Calc'd for $C_{14}H_{22}ONBr_2$: Br, 20.97

Found: Br, 20.9

To a solution of 19.9 g. (0.05 mole) of p-bromophenacyl bromide in 150 cc. of dry benzene in a 500-cc. flask was added 10.1 g., 13.7 cc., (0.1 mole) of di-n-propylamine. The flask was stoppered, shaken, and allowed to stand in the refrigerator for twenty hours. To the suspension was added 300 cc. of dry ether and the crystalline di-n-propylamine hydrobromide was removed by filtration and washed with ether, wt. 8.8 g. (97 percent of the theoretical amount). The filtrate was concentrated on the steam bath to 100 cc. and was added to a solution of 15.3 g. (0.075 mole) of aluminum isopropoxide in 25 cc. of isopropanol in a 200-cc. two-necked glass-jointed flask fitted with a dropping funnel and a helix-packed fractionating column with controlled take-off. Most of the solvent was slowly distilled off and 100 cc. of dry isopropanol was then added through the dropping funnel. The solution was distilled until the distillate no longer contained acetone. The remainder of the solvent was then distilled under reduced pressure. The red-brown semi-solid residue was cooled in ice and treated with 100 cc. of ice-cold 10 percent hydrochloric acid. To this was added 700 cc. of hot water and a small amount of dark red solid remained undissolved. After adding 10 cc. of concentrated hydrochloric acid the solution was cooled and filtered to

---

*The writer wishes to thank Mr. J. D. Draper for this analysis.

remove the undissolved impurity. The filtrate was cooled by means of an ice bath and made strongly alkaline with ice-cold potassium hydroxide solution, causing a brown solid to separate. The suspension was extracted with benzene and the benzene extract was washed with water and dried by distilling into a moisture-point receiver. After concentrating to 100 cc. the solution was saturated with dry hydrogen bromide and tan crystals separated, but later dissolved. Addition of dry ether caused the separation of an oil which on cooling with ice became crystalline. The ether-benzene supernatent liquor was decanted and the crystalline material was crystallized from ethanol-ether, yielding 10.7 g. (56 percent of the theoretical amount) of light tan crystals of α-(p-bromophenyl)-β-di-n-propylaminoethanol hydrobromide.

α-(p-Bromophenyl)-β-piperidylethanol Hydrochloride (LII).

To a solution of 13.9 g. (0.05 mole) of p-bromophenacyl bromide in 150 cc. of dry benzene in 200-cc. flask was added 8.5 g., 9.9 cc., (0.1 mole) of freshly distilled piperidine. The flask was stoppered, shaken, and allowed to stand in the refrigerator for twenty-four hours. The crystalline piperidine hydrobromide was removed by filtration and washed with a little dry benzene, wt. 8.3 g. (100 percent of the theoretical amount). The filtrate was concentrated on the steam bath to 100 cc. and added to a solution of 15.3 g. (0.075 mole) of aluminum isopropoxide in 75 cc. of dry isopropanol in a 200-cc. two-necked glass-jointed flask fitted with a dropping funnel and helix-packed fractionating column with controlled take-off. Most of the solvent was distilled, 100 cc. of dry isopropanol was added through the dropping funnel, and the distillation continued until the distillate gave a negative test with 2,4-dinitrophenylhydrazine reagent.

The remainder of the solvent was removed by distillation at 20 mm. and the residual red-brown product was cooled by means of an ice bath and treated with 100 cc. of ice-cold 10 percent hydrochloric acid. A tan precipitate separated. Addition of 800 cc. of warm water dissolved all except a small amount of dark-colored gummy material. The solution was filtered, cooled in ice, and made strongly alkaline with ice-cold potassium hydroxide solution. A tan solid separated. The suspension was shaken with benzene and the precipitate dissolved. The benzene extract was washed with water and dried by distilling into a moisture-point receiver.

The dry benzene solution was saturated with dry hydrogen chloride and a cream-colored precipitate formed. After adding 200 cc. of dry ether the α-(p-bromophenyl)-β-piperidylethanol hydrochloride was removed by filtration, wt. 13.0 g. (81.2 percent of the theoretical amount). Recrystallization from absolute ethanol yielded colorless crystals, m.p. 237.7-238.2°.

Analysis: Calc'd for $C_{13}H_{19}ONBrCl$: C, 48.69; H, 5.97

Found*: C, 48.48; H, 6.09

* C, 48.59; H, 6.10

Volhard titration of ionizable halogen:

Calc'd for $C_{13}H_{19}ONBrCl$: Cl, 11.06

Found: Cl, 11.0

<u>α-(p-Bromophenyl)-β-di-n-butylaminoethanol Hydrobromide (LIII)</u>. To a solution of 13.9 g. (0.05 mole) of p-bromophenacyl bromide in 150 cc. of dry benzene in a 200-cc. flask was added 12.9 g. (0.1 mole) of di-n-

---

*The writer wishes to thank Mr. J. D. Draper for this analysis.

butylamine. The flask was stoppered, shaken, and cooled by means of an ice bath. After three hours the crystalline precipitate of di-n-butylamine hydrobromide was removed by filtration and washed with a little dry benzene, wt. 9.1 g. The filtrate was treated with 200 cc. of dry ether and 0.6 g. more of di-n-butylamine hydrobromide was obtained, giving a total yield of 9.6 g. (92 percent of the theoretical amount). The filtrate and washings were concentrated to a small volume and placed in a 200-cc. two-necked glass-jointed flask fitted with a dropping funnel and helix-packed fractionating column with controlled take-off, and 15.3 g. (0.075 mole) of aluminum isopropoxide was added. Most of the benzene was slowly distilled off, dry isopropanol was added through the dropping funnel, and the distillation continued until the distillate gave a negative test with 2,4-dinitrophenylhydrazine reagent. The remainder of the solvent was removed by distillation in vacuo. The residue was decomposed with cold 10 percent hydrochloric acid, causing a large amount of dark red oil to separate. The red oil was extracted with ether, leaving a pale yellow aqueous layer. The acid solution was chilled and made strongly alkaline with cold potassium hydroxide solution and a small amount of brown oil separated. The oil was extracted with benzene, the benzene solution was washed with sodium chloride solution, and dried by distilling into a moisture-point receiver. The dry solution was saturated with dry hydrogen bromide and a small amount of oil separated. The benzene was removed by distillation, leaving a very small amount of brown crystalline residue.

To a solution of 13.9 g. (0.05 mole) of p-bromophenacyl bromide in 150 cc. of dry benzene in a 200-cc. flask was added 12.9 g. (0.1 mole) of di-n-butylamine. The flask was stoppered, shaken, and allowed to stand in the refrigerator for twelve hours. To the suspension was added 25 cc. of dry ether and the crystalline di-n-butylamine hydrobromide was removed

by filtration and washed with dry ether, wt. 9.9 g. (89 percent of the theoretical amount). The filtrate and washings were distilled to a small volume and distilled with 15.9 g. (0.075 mole) of aluminum isopropoxide as described in the preceding paragraph. All the solvent was removed under reduced pressure, and the residual oil was acidified with cold 10 percent hydrochloric acid, causing a large amount of red oil to separate. The oil was extracted with ether and the aqueous solution was made strongly alkaline with cold potassium hydroxide solution. The small amount of brown oil which separated was extracted with benzene, and the benzene extract was washed with water and dried by distilling into a moisture-point receiver. The dry benzene solution was saturated with dry hydrogen bromide, dry ether was added, but nothing separated from solution. The solution was distilled to dryness and a small amount of oily residue remained.

To a solution of 14.9 g. (0.05 mole) of p-bromophenacyl bromide in 150 cc. of dry benzene in a 500-cc. flask was added 17.9 g. (0.1 mole) of di-n-butylamine. The flask was stoppered, shaken, and allowed to stand in the refrigerator for fourteen hours. The reaction mixture was treated with 300 cc. of dry ether and the crystalline di-n-butylamine hydrobromide removed by filtration and washed with dry ether, wt. 10.1 g. (96 percent of the theoretical amount). The filtrate and washings were concentrated to 100 cc., transferred to a 200-cc. two-necked glass-jointed flask fitted with a dropping funnel and helix-packed fractionating column with controlled take-off, and 15.9 g. (0.075 mole) of aluminum isopropoxide and a wad of glass wool were added. The solution was slowly distilled under reduced pressure. 75 cc. of dry isopropanol was added through the dropping funnel, and the distillation continued until all the solvent had distilled.

The bath temperature was 75° and the distillate came over at 77-78°. The residue was chilled by means of an ice bath and acidified with 100 cc. of ice-cold 10 percent hydrochloric acid, adding excess ice. A large amount of dark brown oil separated.

To a solution of 14.5 g. (0.071 mole) of aluminum isopropoxide in 100 cc. of dry isopropanol in a 200-cc. two-necked glass-jointed flask, fitted with a dropping funnel and helix-packed fractionating column with controlled takeoff, was added 11.6 g. (0.0285 mole) of ω-di-n-butylamino-p-bromoacetophenone hydrobromide. The resulting colorless solution was slowly distilled until 60 cc. of distillate had collected. At this point the distillate gave a negative test with 2,4-dinitrophenylhydrazine reagent. The reaction mixture was still colorless. The remainder of the solvent was removed by distillation at reduced pressure, leaving a colorless semi-solid residue. The residue was cooled by means of an ice bath, acidified with 100 cc. of ice-cold 10 percent hydrochloric acid, and the resulting suspension was completely dissolved by adding 700 cc. of water, yielding a colorless solution. The solution was cooled with ice and made strongly alkaline with ice-cold potassium hydroxide solution, causing a white solid to separate after the aluminum hydroxide, which first precipitated, redissolved. The suspension was extracted with five 50-cc. portions of benzene, and the colorless benzene extract was washed with water and then dried by distilling into a moisture-point receiver. The dry benzene solution was concentrated to 150 cc. and then saturated with dry hydrogen bromide. To this was added 350 cc. of dry ether, and a colorless oil separated. After standing over night in the refrigerator, the oil completely changed to colorless crystals which were removed by filtration, weight 10.8 g. (93 percent of the theoretical amount), m.p. 112-114°. The α-(p-bromophenyl)-β-di-n-butylaminoethanol

hydrobromide was crystallised from absolute ethanol-ether to a constant melting point of 113.0-114.0° (winters 110.0°).

Analysis: Calc'd for $C_{16}H_{27}ONBr_2$: C, 46.96; H, 6.65

Found*: C, 46.90; H, 6.76

* C, 46.92; H, 6.70

Volhard titration of ionizable halogen:

Calc'd for $C_{16}H_{27}ONBr_2$: Br, 19.54

Found: Br, 19.6

---

*The writer wishes to thank Mr. J. D. Draper for this analysis.

LITERATURE CITED

1P. Aeh and Hofe, United States Patent 2,065,879 (1936).

2. Africa, Dy and Soriano, Acta Medica Phillippina, 1, 19 (1939).

3. Ahluwalia, Keshhar and Ray, J. Indian Chem. Soc., 9, 215-223 (1932); Chem. Abs., 26,5568 (1932)

4. Ainley and King, Proc. Roy. Soc. 125B, 60 (1938).

5P. Altman, British Patent 504,024 (1939).

6. Altman, Rec. Trav. Chim., 57, 941-63 (1938); Quart. Journ. Pharm., Pharmacol., 11, 784 (1938).

7P. Andersag, United States Patent 2,187,847 (1940); Chem. Abs. 34, 3889 (1940).

8P. Andersag, Breitner and Jung, German Patent 689,692 (1939); Chem. Abs. 36, 4973 (1942).

9P. Andersag, Breitner and Jung, United States Patent 2,233,970 (1941); Chem. Abs., 35, 3771 (1941).

10. Anspon, private communication.

11. Bachmann and Boatner, J. Am. Chem. Soc., 58, 857, 2097 (1936).

12. Bankeberg, J. Chem. Soc., 1984 (1932).

13. Baldwin, J. Chem. Soc., 2959-65 (1929).

14. Baldwin and Robinson, J. Chem. Soc., 1264-7 (1934).

15. Baltzly and Buck, J. Am. Chem. Soc., 62, 164 (1940).

16. Barber and Slack, J. Am. Chem. Soc., 65, 1776-7 (1943).

17. Barnett and Smiles, J. Chem. Soc., 962 (1910).

18. Barnum and Hamilton, J. Am. Chem. Soc., 64, 540-2 (1942).

19P. Basford, Rose and Imperial Chemical Industries, Ltd., British Patent 544,190 (1942).

20. Basu and Das-Gupta, J. Indian Chem. Soc., 14, 468-73 (1937); Chem. Abs., 32, 4989-90 (1938).

21. Basu and Das-Gupta, J. Indian Chem. Soc., 15, 160-4 (1938); Chem. Abs., 32, 7099 (1938).

22. Basu and Das-Gupta, J. Indian Chem. Soc., 16, 100-6 (1939); Chem. Abs., 33, 5052 (1939).

23. Basu and Das-Gupta, J. Indian Chem. Soc., 16, 301-4 (1939); Chem. Abs., 34, 1021 (1940).

24. Beer, J. Gen. Chem. (U.S.S.R.), 9, 2158-61 (1939); Chem. Abs., 34, 4148 (1940).

25P. Behnisch, Klarer and Mietzsch, United States Patent 2,248,911 (1941).

26. Bentley, Haworth and Perkin, J. Chem. Soc., 161 (1896).

27. Berkenheim and Lure, J. Gen. Chem. (U.S.S.R.), 6, 1043-56 (1936); Chem. Abs., 31, 1780 (1937).

28. Berkenheim and Spasokukotskii, J. Gen. Chem. (U.S.S.R.), 11, 541-4 (1941); Chem. Abs., 35, 6962 (1941).

29. Bernthsen, Ann., 230, 93 (1885); Ber., 16, 2896 (1883).

30. Bernthsen, Ann., 230, 106 (1885).

31. Bischoff, Ber., 31, 2678 (1898).

32. Blicke, Parke and Jenner, J. Am. Chem. Soc., 62, 3316-19 (1940).

33. Bobranski and Boguslaw, Arch. Pharm., 277, 75-86 (1935).

34P. Bockmühl, Krebs and Ehrhart, United States Patent 1,936,547 (1933).

35P. Bockmühl, Krebs and Ehrhart, United States Patent 2,016,480 (1935).

36. Boehmer, Rec. trav. chim., 56, 901-6 (1937).

37P. Boëseken and Bijlsma, United States Patent 2,231,612 (1941); British Patent 454,525 (1936).

38. Borsche, Stackmann and Makaroff, Ber., 49, 2222-43 (1916).

39. Bovet, Benoit and Altman, Bull. Soc. Path. exot., 27, 236-42 (1934).

Bovet and Demanche, Ann. Inst. Pasteur, 51, 528-34 (1933).

41. Boyd, Am. J. Hyg., 6, 173 (1926).

42. Brahmachari, Calcutta Med. J., 34, 327-34 (1938); Chem. Abs., 33, 9448 (1939).

43. Brahmachari and Bhattacharjee, J. Indian Chem. Soc., 8, 7-10 (1931); Chem. Abs., 25, 3999 (1931).

44. Brahmachari, Bhattacharjee, Banerjee and Maity, J. Pharmacol., 39, 413-5 (1930); Chem. Abs., 24, 5875 (1930).

45. Brahmachari and Das-Gupta, J. Indian Chem. Soc., 9, 37-42 (1932); Chem. Abs., 26, 3797 (1932).

46. Brahmachari and Das-Gupta, J. Indian Chem. Soc., 9, 207-9 (1932); Chem. Abs., 26, 5566 (1932).

47. Brahmachari, Das-Gupta and Bhattacharjee, J. Indian Chem. Soc., 8, 315-7 (1931); Chem. Abs., 26, 458 (1932).

48. Buchmann and Hamilton, J. Am. Chem. Soc., 64, 1357-60 (1942).

49. Burkhalter, Jones, Holcomb and Sweet, J. Am. Chem. Soc., 65, 2012-15 (1943).

50. Burger, J. Am. Chem. Soc., 60, 1536 (1938).

51. Burger, J. Chem. Education, 18, 58-61 (1941).

52. Burger and Mosettig, J. Am. Chem. Soc., 58, 1857 (1936).

53. Buttle, Trans. Roy. Soc. Trop. Med. Hyg., 33, 141 (1939).

54. Buttle, Henry, Solomon, Trevan and Gibbs, Biochem. J., 32, 47-58 (1938).

55. Buttle, Henry and Trevan, Biochem. J., 28, 426 (1934).

56. Cade, Chem. and Met. Eng., 29, 319 (1923).

57P. Callsen, Re-issue 16,394 of United States Patent 1,572,768 (1926).

58P. Carpmael, British Patent 267,169 (1927).

59P. Carpmael, British Patent 286,087 (1926).

60P. Carpmael, British Patent 302,984 (1926).

61P. Carpmael, British Patent 302,985 (1928).

62. Chatterjee, J. Chem. Soc., 2965-8 (1929).

63. Cherntsov and Drozdov, J. Gen. Chem. (U.S.S.R.), 9, 1435-40 (1939); Chem. Abs., 34, 1667 (1940).

64P. Child and Pyman, British Patent 344,166 (1930).

65. Child and Pyman, J. Chem. Soc., 2010-21 (1929).

66. Child and Pyman, J. Chem. Soc., 36-49 (1921).

67. Chopra and Basu, J. Malaria Inst. India, 2, 153-4 (1939); Chem. Abs., 33, 7897 (1939).

68. Chopra and Das-Gupta, Indian Med. Gaz., 74, 201 (1939).

69. Chopra, Hayter and Sen, Indian Med. Gaz., 74, 658 (1939).

70. Christophers and Fulton, Ann. Trop. Med., 32, 257-78 (1938).

71. Claus, Ber. 14, 2366 (1881).

72. Clemo and Hook, J. Chem. Soc., 608-9 (1936).

73. Clemo, Mollwain and Morgan, J. Chem. Soc., 610-1 (1936).

74. Clibbens and Hierenstein, J. Chem. Soc., 1491 (1915).

75. Coggeshall, Am. J. Trop. Med., 18, 715-21 (1938).

76. Coggeshall, Proc. Soc. Exptl. Biol. Med., 38, 768-73 (1938).

77. Coggeshall, Maier and Best, J. Am. Med. Assoc., 117, 1077-81 (1941).

78. Cohen, Cooper and Marshall, Proc. Roy. Soc., 108B, 130 (1931).

79. Cohen and King, Proc. Roy. Soc., 125B, 49-60 (1938).

80. Collier and Krause, Z. Hyg., 110, 522 (1929).

81. Coulthard, Levene and Pyman, Biochem. J., 27, 727 (1933).

82. Crossley, Northey and Hultquist, J. Am. Chem. Soc., 60, 2217 (1938).

83. Dannenroeder and Shriner, J. Am. Chem. Soc., 58, 1610-2 (1936).

84. Das-Gupta, J. Indian Chem. Soc., 16, 364-8 (1939); Chem. Abs., 34, 2379 (1940).

85. Derick and Bissell, J. Am. Chem. Soc., 38, 2483 (1916).

86. Desai, J. Indian Inst. Sci., 7, 235-51 (1924).

87. Di Mauro, Gazz. ospedali clin., 60, 544 (1939); Chem. Abs., 33, 8810 (1939).

88. Domingues, Rev. Farm. (Buenos Aires), 73, 82 (1932); Chem. Abs., 26, 4102 (1932).

89. Dreadov, J. Gen. Chem. (U.S.S.R.), 7, 219 (1937); Chem. Abs., 31, 4320 (1937).

90. Dreadov, J. Gen. Chem. (U.S.S.R.), 7, 1668-74 (1937); Chem. Abs., 32, 160 (1938).

91. Drozdov, J. Gen. Chem. (U.S.S.R.), 8, 1192-3 (1938); Chem. Abs., 33, 4251 (1939).

92. Drozdov and Stavrovskaya, J. Gen. Chem. (U.S.S.R.), 9, 409-14 (1939); Chem. Abs., 34, 103 (1940).

93. Drozdov and Stavrovskaya, J. Gen. Chem. (U.S.S.R.), 9, 1642-6 (1939); Chem. Abs., 34, 3703 (1940).

94. du Feu, McQuillin and Robinson, J. Chem. Soc., 53 (1937).

95P. Easson and Pyman, British Patent 365,281 (1931).

96. Easson and Pyman, J. Chem. Soc., 2991-3001 (1931).

97. Easson and Pyman, J. Chem. Soc., 1306-12 (1932).

98. Ehrenstein, Am. J. Pharm., 114, No. 12, 456-82 (1942).

99P. Einhorn, German Patent 55,119 (1890).

100. Eisleb, "Medicine in its Chem. Aspects," Vol. III (1938), 39-57.

101P. Eisleb, United States Patent 1,845,403 (1932).

102P. Eisleb, United States Patent 1,967,356 (1934).

103. Engler and Zielke, Ber., 22, 203 (1889).

104P. Ewins and Ashley, British Patent 510,097 (1939); Chem. Abs., 34, (1940).

105P. Ewins and Phillips, British Patent 531,857 (1941).

106. Faget, Palmer and Sherwood, U. S. Public Health Repts., 53, 1364 (1938); Chem. Abs., 32, 8578 (1938).

107P. Farbwerke vorm. Meister Lucius and Brüning, British Patent 167,781 (1922).

108P. Farbwerke vorm. Meister Lucius and Brüning, British Patent 199,870 (1923).

109P. Farbwerke vorm. Meister Lucius and Brüning, German Patent 364,035 (1922).

110. Fel'dman and Kopelievich, Arch. Pharm., 273, 438-96 (1935); Chem. Abs., 30, 1378 (1936).

111. Fieser, "Experiments in Organic Chemistry," Heath, p. 425.

112. Findlay, "Recent Advances in Chemotherapy," London, 1930.

113. Finzi, Gazz. chim. ital., 62, 175-89 (1932); Chem. Abs., 26, 4338 (1932).

114. Fischl and Schlossberger, "Handbook of Chemotherapy," Vol. 1, 1933.

115. Fourneau, Stefanopoulo, Benoit, Lestrange and Melville, Ann. Inst. Pasteur, 44, 503-33 (1930).

116. Fourneau, Tréfouel and Benoit, Ann. Inst. Pasteur, 44, 719-51 (1930).

117. Fourneau, Tréfouel, Tréfouel, Bovet and Benoit, Ann. Inst. Pasteur, 46, 514 (1931).

118. Fourneau, Tréfouel, Tréfouel, Bovet and Benoit, Ann. Inst. Pasteur, 50, 731-44 (1933).

119. Fox and Bogert, J. Am. Chem. Soc., 61, 2013 (1939).

120. Frankel, Tritt, Mehrer and Hereuhmann, Ber., 58, 544 (1925).

121. Fulton, Ann. Trop. Med., 31, 7-14 (1937).

122. Fulton, Ann. Trop. Med., 34, 53-66 (1940).

123. Gabriel and Meiner, Ber., 21, 2671 (1888).

124. Gerchuk, J. Gen. Chem. (U.S.S.R.), 11, 731-8 (1941).

125. Ghosh, J. Indian Chem. Soc., 14, 113-5 (1937); Chem. Abs., 31, 5362 (1937).

126. Ghosh, J. Indian Chem. Soc., 15, 240-2 (1938); Chem. Abs., 32, 9087 (1938).

127. Gibbs and Henry, J. Chem. Soc., 1234 (1939).

128. Gibson and Levin, J. Chem. Soc., 2388 (1931).

129. Giemsa and Halberkann, Ber., 52, 906 (1919).

130. Giemsa and Oesterlin, Arch. Schiffs-u. Tropen-Hyg., 37, (4) 32 (1933); Chem. Abs., 28, 4475 (1935).

131P. Giemsa, Oesterlin and Putzer, United States Patent 1,972,988 (1934); German Patent 551,094 (1932).

132. Giemsa, Weise and Tropp, Arch. Schiffs-u. Tropen-Hyg., 30, 334-47 (1926); Chem. Abs., 21, 134 (1927).

133. Glyn-Hughes, Lourie and Yorke, Ann. Trop. Med., 32, 103-7 (1938).

134P. Goissedet and Despois, United States Patent 2,092,114 (1937).

135. Goodall and Kermack, J. Chem. Soc., 1546-50 (1936).

136. Goodson, Henry and McFie, Biochem. J., 24, 874-90 (1930).

137. Guha and Mukherji, Current Sci., 12, 148-9 (1943).

138. Guha, Rao and Verghese, Current Sci., 12, 82-3 (1943); Chem. Abs., 37, 5696 (1943).

139. Gunn and Marshall, Proc. Roy. Soc. Edinburgh, 40, 140-9 (1920).

140. Guttmann and Ehrlich, Berl. Klin. Wschr., 28, 593 (1891).

141. Hal'perin, Med. Parasitol. Parasitic Diseases (U.S.S.R.), 9, 44-53 (1940); Chem. Abs., 36, 1674 (1942).

142. Haq, Kapur and Ray, J. Chem. Soc., 1087 (1933).

143P. Hata, Matsumura and Ishihara, United States Patent 2,083,908 (1937).

144. Haussler, Schweiz. Apoth. Ztg., 56, 207 (1918).

145. Headlee, Collett and Lazzell, J. Am. Chem. Soc., 55, 1066 (1933).

146. Hegner, Shaw and Manwell, Am. J. Hyg., 8, 564-81 (1928).

147. Hegner, West and Dobler, Am. J. Hyg., 34, 132-9 (1941).

148P. Henecka, United States Patent 2,112,961 (1938).

149P. Henecka and Andersag, United States Patent 2,082,160 (1937).

150. Henry, J. Soc. Chem. Ind., 55, 111T (1936).

151. Holcomb and Hamilton, J. Am. Chem. Soc., 64, 1309-11 (1942).

152. Horlein, Arch. Schiffs-u. Tropen-Hyg., 30, 305 (1926).

153. Horlein, Arch. Schiffs-u. Tropen-Hyg., 32, 382 (1928).

154. Horlein, Naturwissenschaften, 14, 1160-2 (1926).

155. Hughes, Lions, Maunsell and Wright, J. Proc. Roy. Soc. N. S. Wales, 71, 428-34; Chem. Abs., 33, 613 (1939).

156. Hyde, Browning and Adams, J. Am. Chem. Soc., 50, 2287 (1928).

157P. I. G. Farbenindustrie, British Patent 267,457 (1925); Chem. Abs., 22, 1216 (1928).

158P. I. G. Farbenindustrie, British Patent 274,058 (1925).

159P. I. G. Farbenindustrie, British Patent 275,277 (1927).

160P. I. G. Farbenindustrie, British Patent 275,622.

161P. I. G. Farbenindustrie, British Patent 276,012 (1921).

162P. I. G. Farbenindustrie, British Patent 282,143 (1926).

163P. I. G. Farbenindustrie, British Patent 282,453 (1929).

164P. I. G. Farbenindustrie, British Patent 300,279.

165P. I. G. Farbenindustrie, British Patent 301,401 (1928); Chem. Zentr., 1929 I, 1968.

166P. I. G. Farbenindustrie, British Patent 304,280 (1930).

167P. I. G. Farbenindustrie, British Patent 321,738 (1928); Chem. Abs., 24, 2837 (1930).

168P. I. G. Farbenindustrie, British Patent 367,952 (1932); Chem. Abs., 27, 2161 (1933); German Patent 540,699 (1929).

169P. I. G. Farbenindustrie, British Patent 373,624 (1931).

170P. I. G. Farbenindustrie, British Patent 409,728 (1934).

171P. I. G. Farbenindustrie, British Patent 450,254 (1936).

172P. I. G. Farbenindustrie, British Patent 466,505 (1936); German Patent 642,758 (1937).

173P. I. G. Farbenindustrie, British Patent 481,874 (1938); Chem. Abs., 32, 6261 (1938); United States Patent 2,231,844 (1941); German Patent 669,806 (1939).

174P. I. G. Farbenindustrie, German Patent 498,661 (1930).

175P. I. G. Farbenindustrie, German Patent 511,466 (1930); British Patent 321,974 (1929).

176P. I. G. Farbenindustrie, German Patent 533,691 (1931); British Patent 347,515 (1931).

177P. I. G. Farbenindustrie, German Patent 606,497 (1934); United States Patent 2,092,352 (1937).

178P. I. G. Farbenindustrie, German Patent 622,596 (1935).

179P. I. G. Farbenindustrie, German Patent 632,733 (1936).

180P. Imray, British Patent 176,038 (1922).

181. Ing and Manske, J. Chem. Soc., 2348 (1926).

182. Ismail'skii and Simonov, J. Gen. Chem. (U.S.S.R.), 10, 1530-7 (1940); Chem. Abs., 35, 2070 (1941).

183. James, Nicol and Shute, Trans. Roy. Soc. Med. Hyg., 21, 233 (1927-8).

184P. Jensch, German Patent 613,065 (1935); Chem. Abs., 29, 5603 (1935); United States Patent 2,066,730 (1937); British Patent 443,916.

185P. Jensch, United States Patent 1,629,873 (1927).

186P. Jensch, United States Patent 1,790,096 (1931).

187P. Jensch, United States Patent 2,034,983 (1936); British Patent 414,505 (1934); German Patent 591,480 (1934).

188P. Jensch, United States Patent 2,050,971 (1936).

189P. Jensch, United States Patent 2,228,166 (1941).

190P. Jensch and Eisleb, British Patent 283,510 (1929); German Patent 488,630 (1929); United States Patent 1,962,277 (1934).

191P. Jensch and Eisleb, United States Patent 1,782,727 (1930).

192. Jensen and Rothwisch, J. Am. Chem. Soc., 50, 1146 (1928).

193. John and Slowasky, Z. Immunitats, 78, 280-3 (1933).

194. Kalberlah and Schlossberger, Deut. Med. Woch., 44, 1100 (1918).

195. Karrer, Ber., 50, 1499-508 (1917).

196P. "Kantel" tvor. kemi. pr. D. D. and Prelog, British Patent 517,830 (1940); United States Patent 2,192,840 (1940).

197. Kaufmann, Ber., 46, 1823-37 (1913).

198. Kermack and Muir, J. Chem. Soc., 3089-96 (1931).

199. Kermack, Muir and Wight, J. Chem. Soc., 1143-5 (1935).

200. Kermack and Smith, J. Chem. Soc., 1356-61 (1930).

201. Kermack and Smith, J. Chem. Soc., 3096-104 (1931).

202. Kermack and Tebrich, J. Chem. Soc., 314-8 (1940).

203. Kermack and Weatherhead, J. Chem. Soc., 1164-9 (1940).

204. Kermack and Webster, J. Chem. Soc., 213 (1942).

205. Kermack and Wight, J. Chem. Soc., 1421-6 (1935).

206. Kikuth, Deut. Med. Woch., 58, 530 (1932).

207. Kikuth, German Patent 673,150 (1939); British Patent 493,752 (1939).

208. King, Lourie and Yorke, Lancet, 233, 1360 (1937).

209. King and Work, J. Chem. Soc., 1307-15 (1940).

210. Kingsbury, Ann. Rept. of Malaria Advisory Board for 1937, Kuala Lumpur.

211. Knowles and Das-Gupta, Ind. Med. Gaz., 67, 301-20 (1932).

212. Knunyants, Bull. acad. sci. (U.S.S.R.), 153-64 (1934).

213. Knunyants and Benevolenskaya, J. Gen. Chem. (U.S.S.R.), 7, 2471-7 (1937); Chem. Abs., 32, 2119 (1938).

214. Knunyants and Benevolenskaya, J. Gen. Chem. (U.S.S.R.), 7, 2930-3 (1937); Chem. Abs., 32, 5404 (1938).

215. Knunyants and Benevolenskaya, J. Gen. Chem. (U.S.S.R.), 10, 1415 (1940).

216. Knunyants, Cholintsev, Benevolenskaya, Ostrova and Karsanova, Bull. acad. sci. (U.S.S.R.), 159-64 (1934); Chem. Abs., 28, 4837 (1937).

217. Knunyants, Cholintsev and Ostrova, Acad. Des. Sci. De Russie, Comptes Rendus 1, 312 (1934).

218. Koenigsberg, L'Industrie Chimique, 8, 314-6 (1921).

219. Krahler and Burger, J. Am. Chem. Soc., 63, 2367-71 (1941).

220. Krichevskii, Magidson, Mal'perin and Grigorovskii, Ber. ges. Physiol. exptl. Pharmakol., 83, 220 (1937); Chem. Abs., 31, 3203 (1937).

221. Kritchevskii and Sternberg, Z. Immunitats, 80, 439-59 (1933).

222. Kritchevskii, Sternberg and Mal'perin, J. Microbiol., Epidemiol., Immunobiol. (Russ.), 14, 642-54 (1935).

223. Ku and Scheven, Ber., 31, 173-4 (1898).

224. Kwartler and Lucas, J. Am. Chem. Soc., 65, 354-5 (1943).

225. Lamb and White, J. Chem. Soc., 1253-7 (1939).

226. Laun, Ber., 17, 675 (1884).

227. de Leon, U. S. Pub. Health Repts., 52, 1460-3 (1937); Chem. Abs., 32, 1334 (1938).

228. Loesene and Henze, J. Am. Chem. Soc., 64, 1897-1900 (1942).

229. Liu, Chang, Ch'uan and Tan, Chinese Med. J., 59, 575 (1941); Trop. Diseases Bull., 39, 179 (1942).

230. Liu, Chang, Ch'uan and Tan, J. Trop. Med. Hyg., 45, 15-6 (1942).

231. Lockhart and Turner, J. Chem. Soc., 424 (1937).

232F. Loewe, German Patent 380,918 (1923).

233. Lund, Ber., 70, 1520-5 (1937).

234. Magidson and Bobyshev, J. Gen. Chem. (U.S.S.R.), 8, 899-914 (1938).

235. Magidson, Delectorskaya and Lipovich, Arch. Pharm., 272, 74-84 (1934).

236. Magidson and Golovchinskaya, J. Gen. Chem. (U.S.S.R.), 8, 1797 (1938); Chem. Abs., 33, 4993 (1939).

237. Magidson and Grigorovskii, Ber., 69B, 396-412 (1936); Khim. Farm. Prom., 187-8 (1933); Chem. Abs., 30, 3822 (1936).

238. Magidson, Grigorovskii and Hal'perin, J. Gen. Chem. (U.S.S.R.), 8, 56-65 (1938); Chem. Abs., 32, 5405 (1938).

239. Magidson, Grigorovskii, Maksimov and Margolina, Khim. Farm. Prom., (1) 26-34 (1935); Chem. Abs., 30, 1516 (1936).

240. Magidson, Madajewa and Rubtsov, Arch. Pharm., 273, 320-33 (1935); J. Gen. Chem. (U.S.S.R.), 5, 1506-15 (1935); Chem. Abs., 29, 7013 (1935).

241. Magidson and Rubtsov, J. Gen. Chem. (U.S.S.R.), 7, 1896 (1937); Chem. Abs., 32, 564 (1938).

242. Magidson and Strukov, Arch. Pharm., 271, 359-69 (1933).

243. Magidson and Strukov, Arch. Pharm., 271, 569-80 (1933); Chem. Abs., 28, 1770 (1934).

244. Magidson, Strukov, Bobyshev and Terf, J. Applied Chem. (U.S.S.R.), 9, 304-20; Chem. Abs., 30, 5582 (1936).

245. Magidson and Travin, Ber., 69B, 537 (1936).

246. Magidson and Travin, J. Gen. Chem. (U.S.S.R.), 7, 842-52 (1937); Chem. Abs., 31, 5800 (1937).

247. Magidson and Travin, J. Gen. Chem. (U.S.S.R.), 11, 243-53 (1941); Chem. Abs., 35, 7965 (1941).

248. Malkin and Nierenstein, J. Am. Chem. Soc., 52, 1504 (1930).

249. Mannaberg, Deutsch. Arch. Klin. Med., 59, 185 (1897).

250. Mannich and Hof, Arch. Pharm., 265, 589 (1927).

251. Mannich, Lesser and Silten, Ber., 65, 381 (1932).

252. Manske, The Chemistry of Quinolines, Chem. Rev., 30, 113 (1942).

253. Manwell, Counts and Coulston, Proc. Soc. Exptl. Biol. Med., 46, 523-5 (1941).

254. Marchoux, Compt. rend., 180, 617 (1925); Ann. Inst. Pasteur, 39, 197 (1925).

255. Marshall, Physiol. Rev., 22, 190-200 (1942).

256. Marshall, Litchfield and White, J. Pharm. Exptl. Therap., 75, 89-104 (1942).

257. Marvel and du Vigneaud, J. Am. Chem. Soc., 46, 2098 (1924).

258. Marvel, Zartman and Bluthardt, J. Am. Chem. Soc., 49, 2299-303 (1927).

259. Mason and Rose, J. Am. Chem. Soc., 62, 2832 (1940).

260. Matejka and Robinson, J. Chem. Soc., 1322-6 (1934).

261. Mathur and Robinson, J. Chem. Soc., 1520-3 (1933).

262P. Mauss, United States Patent 1,855,302 (1932).

263P. Mauss and Mietzsch, German Patent 553,072 (1932).

264P. Mauss and Mietzsch, German Patent 571,449 (1930); British Patent 363,392 (1931).

265. Mauss and Mietzsch, Klin. Woch., 12, 1276-8 (1933).

266P. Mauss and Mietzsch, United States Patent 2,079,023 (1937).

267P. May, British Patent 452,805 (1935).

268. Meerwein and Schmidt, Ann., 444, 221 (1925).

269. Meisel and Robinson, J. Chem. Soc., 1267 (1934).

270P. Miescher and Urech, United States Patent 1,881,236 (1932).

271P. Mietzsch, German Patent 490,418 (1926); United States Patent 1,727,480 (1939).

272. Mietzsch and Mauss, Angew. Chem., 47, 633 (1934); Chem. Abs., 28, 7360 (1934).

273P. Mietzsch and Mauss, British Patent 407,953 (1935); United States Patent 2,082,171 (1937).

274P. Mietzsch and Mauss, British Patent 441,007 (1935); German Patent 631,504 (1936); United States Patent 2,077,249 (1937).

275P. Mietzsch and Mauss, British Patent 441,132 (1936); Chem. Zentr., 1936 I, 4467.

276P. Mietzsch and Mauss, British Patent 466,505 (1935).

277P. Mietzsch and Mauss, German Patent 642,758 (1937).

278P. Mietzsch and Mauss, United States Patent 2,113,357 (1938).

279P. Mietzsch and Mauss, United States Patent 2,121,207 (1938).

280. Miki and Robinson, J. Chem. Soc., 1467-9 (1933).

281. Moncorvo, Therap. Monatsh., 11, 501 (1897).

282. Monti and Procopio, Gazz. Chim. Ital., 63, 724-30 (1933); Chem. Abs., 28, 2357 (1934).

283. Monti and Simonetti, Gazz. Chim. Ital., 70, 369-74 (1940); Chem. Abs., 35, 3241 (1941).

284P. Morgan and Stewart, British Patent 519,660 (1940).

285. Mosettig and van de Kamp, J. Am. Chem. Soc., 55, 3442-8 (1933).

286. Mosettig and van de Kamp, J. Am. Chem. Soc., 55, 3448-53 (1933).

287. Mühlens, Arch. Schiffs-u. Tropen-Hyg., 30, (3) 31 (1926).

288. Mühlens, Naturwissenschaften, 14, 1162-6 (1926).

289. Murray and Turner, J. Chem. Soc., 856 (1934).

290. Nandi, J. Indian Chem. Soc., 17, 449-52 (1941); Chem. Abs., 35, 2146 (1941).

291. Nandi, Proc. Indian Acad. Sci., 12A, 1-19 (1940); Chem. Abs., 13, 143 (1919).

292. Narang, Ray and Singh, J. Indian Chem. Soc., 11, 427-31 (1934); Chem. Abs., 29, 163 (1935).

293. Nanok and Picado, Arch. Schiffs-u. Tropen-Hyg., 34, 29-42 (1930); Chem. Abs., 24, 3275 (1930).

294. Ochiai, Eiji and Katada, J. Pharm. Soc. Japan, 60, 543-50 (1940); Chem. Abs., 35, 1735 (1941).

295. Oesterlin, Arch. Schiffs-u. Tropen-Hyg., 41, 720-3 (1937); Chem. Abs., 33, 4667 (1939).

296. "Organic Syntheses," 14, 20 (1934).

297. "Organic Syntheses," Coll. Vol. I, p. 8.

298. "Organic Syntheses," Coll. Vol. I, p. 30.

299. "Organic Syntheses," Coll. Vol. I, p. 109.

300. "Organic Syntheses," Coll. Vol. I, p. 119.

301. "Organic Syntheses," Coll. Vol. I, p. 127.

302. "Organic Syntheses," Coll. Vol. I, p. 426.

303. "Organic Syntheses," Coll. Vol. I, p. 435.

304. "Organic Syntheses," Coll. Vol. I, p. 463.

305. "Organic Syntheses," Coll. Vol. I, p. 533.

306. "Organic Syntheses," Coll. Vol. II, p. 88.

307. "Organic Syntheses," Coll. Vol. II, p. 223.

308. "Organic Syntheses," Coll. Vol. II, p. 446.

309. "Organic Syntheses," Coll. Vol. II, p. 480.

310. Perkin and Bellenot, Ber., 17, 326 (1884).

311P. Perkin and Clemo, British Patent 214,756 (1923).

312. Pomndorf, Z. Angew. Chem., 39, 138 (1926).

313. Prelog, Seiwerth, Heimbach-Juhasz and Stern, Ber., 74B, 647-52 (1941); Naturwissenschaften, 28, 759 (1940); Chem. Abs., 35, 7970 (1941).

314. Pyman, Chemistry and Industry, 580-5 (1935).

315P. Pyman and Levene, United States Patent 2,043,622 (1936); British Patent 359,180 (1931).

316. Rabe, Ann., 492, 242 (1932).

317. Rabe, Ber., 41, 62 (1908).

318. Rabe and Hagen, Ber., 74B, 636-47 (1941); Chem. Abs., 35, 7967 (1941).

319. Rabe, Hutenberg, Schultze and Volger, Ber., 64B, 2487-500 (1931).

320. Rabe and Kindler, Ber., 51, 466 (1918).

321. Rabe and Kindler, Ber., 51, 1360 (1918).

322. Rabe and Kindler, Ber., 52, 1842 (1919).

323. Rabe, Pastermack and Kindler, Ber., 50, 144-56 (1917).

324. Rabe and Risa, Ann., 496, 151 (1932).

325. Rabe and Schultze, Ber., 66, 120 (1933).

326. Ray, Ahluwalia and Keshhar, J. pract. Chem., 136, 117-9 (1933); Chem. Abs., 27, 1879 (1933).

327P. Reitmann, United States Patent 2,057,978 (1936).

328. Robinson and Tomlinson, J. Chem. Soc., 1524-30 (1934).

329. Roehl, Arch. Schiffs-u. Tropen-Hyg., 30, (3) 11 (1926).

330. Roehl, Naturwissenschaften, 14, 1156-9 (1926).

331. Rogers, Brit. Med. J., (1), 6-8 (1917); Chem. Abs., 11, 1209 (1917).

332P. Rothmann and Fricker, German Patent 602,049 (1934); Chem. Abs., 29, 474 (1935).

333. Roy, J. Indian Med. Assoc., 11, 341 (1941).

334. Ruberg and Shriner, J. Am. Chem. Soc., 57, 1581 (1935).

335. Rubin and Day, J. Org. Chem., 5, 54 (1940).

336. Rubtsov, J. Gen. Chem. (U.S.S.R.), 9, 1493 (1939); Chem. Abs., 34, 2850 (1940).

337. Ruzicka, Seidel and Leibl, Helv. Chim. Acta, 7, 995-1012 (1924).

338. Sah, J. Am. Chem. Soc., 64, 1487-8 (1942).

339P. Schoeller and von Schickh, United States Patent 2,002,280 (1935).

340. Schönhöfer, "Medicine in its Chemical Aspects," Vol. III (1938), 62-8.

341P. Schönhöfer, United States Patent 1,902,109 (1933).

342P. Schönhöfer and Semecka, German Patent 583,207 (1933); British

Patent 390,831 (1933); United States Patent 2,042,023 (1936).

343P. Schönhöfer and Heneska, United States Patent 2,068,824 (1937); British Patent 390,831.

344. Schulemann, Brit. Med. J., 1, 100 (1932).

345. Schulemann, Lancet, 222, 134 (1932).

346P. Schulemann, Mietzsch and Wingler, United States Patent 1,879,540 (1932).

347P. Schulemann, Mietzsch and Wingler, United States Patent 1,879,541 (1932).

348P. Schulemann, Mietzsch and Wingler, United States Patent 1,889,704 (1932).

349P. Schulemann, Mietzsch and Wingler, United States Patent 1,902,104 (1933).

350P. Schulemann, Schönhöfer and Mietzsch, United States Patent 1,747,532 (1930).

351P. Schulemann, Schönhöfer and Wingler, British Patent 282,510 (1926); Chem. Abs., 22, 3735 (1938); United States Patent 1,903,196 (1933).

352P. Schulemann, Schönhöfer and Wingler, German Patent 486,079 (1929).

353P. Schulemann, Schönhöfer and Wingler, German Patent 490,275 (1930).

354. Schulemann, Schönhöfer and Wingler, Klin. Woch., 11, 381 (1932).

355. Schulemann, Schönhöfer and Wingler, Proc. Roy. Soc. Med., 25, (1) 895-905 (1931-2).

356P. Schulemann, Schönhöfer and Wingler, United States Patent 1,747,531 (1930).

357P. Schulemann, Schönhöfer and Wingler, United States Patent 1,760,781 (1930).

358P. Schulemann, Wingler and Mietzsch, German Patent 488,945 (1929).

359P. Schulemann, Wingler and Mietzsch, United States Patent 1,766,403 (1930).

360. Seelig and Singh, Records Malaria Survey India, 6, 171 (1936); Chem. Abs., 30, 6826 (1936).

361. Sergent and Sergent, Ann. Inst. Pasteur, 35, 125-41 (1921).

362. Seshadri, J. Chem. Soc., 2952-9 (1929).

363. Sherndal, Chem. and Eng. News, 21, 1154-8 (1943).

364. Shimokawa, Chem. Abs., 31, 6737 (1937).

365. Simonov, J. Gen. Chem. (U.S.S.R.), 10, 1588-99 (1941); Chem. Abs. 35, 2370 (1941).

366. Singh and Singh, J. Malaria Institute India, 2, 181 (1939).

367. Sinton, Hutton and Shute, Ann. Trop. Med., 31, 37-44 (1939).

368. Sioli, Arch. Schiffs-u. Tropen-Hyg., 30, (3) 18 (1926).

369. Sioli, Naturwissenschaften, 14, 1162-6 (1926).

370. Sisseoff, Ber., 40, 4546 (1907).

371. Slater, J. Chem. Soc., 1209-15 (1930).

372. Slater, J. Chem. Soc., 107-113 (1931).

373. Slater, J. Chem. Soc., 1938-43 (1931).

374. Sletta and Behnisch, Ber., 68B, 754-61 (1935).

375P. Society of Chemical Industry in Basle, British Patent 349,761 (1931).

376P. Society of Chemical Industry in Basle, British Patent 355,017 (1930).

377. Sternberg, Z. Ges. Exptl. Med., 79, 548 (1932); Chem. Abs., 26, 4879 (1932).

378. Stevens and Tucker, J. Chem. Soc., 2140 (1923).

379P. Stoll, United States Patent 1,447,400 (1923).

380. Surbek, Geneeskund. Tijdschr. Nederland.-Indië, 62, 741-5 (1922); Chem. Abs., 17, 1670 (1923).

381. Taliaferro and Cannon, Am. J. Hyg., 19, 335-42 (1934).

382. Tate and Vincent, Parasitology, 25, 411-27 (1933).

383. The History of Cinchona, Brit. Med. J., 299 (1942); Chemistry and Industry, 61, 218 (1942).

384. Tomlinson, J. Chem. Soc., 158 (1939).

385. Ullmann, Ber., 39, 309 (1906).

386. Untermohlen and Hamilton, J. Am. Chem. Soc., 63, 156 (1941).

387. Van der Kleien, Nederland. Tijdschr. Geneeskunde., 81, 2905-6 (1937); Chem. Abs., 31, 5368 (1937).

388P. van Schelven, British Patent 388,037 (1932).

389. Von Oettingen, "Therapeutic Agents of the Quinoline Group," The Chemical Catalog Company, N. Y., 1933.

390. Vosswinckel, Ber., 45, 1004 (1912).

391. Walker, J. Chem. Soc., 686-92 (1940).

392. Walker, J. Chem. Soc., 1304-7 (1940).

393. Walker and Van Dyke, Proc. Soc. Exptl. Biol. Med., 48, 368-72 (1941).

394. Walls, J. Chem. Soc., 1405 (1935).

395. Whittingham, Proc. Roy. Soc. Med., 18, War Section 23-32 (1925).

396P. Wibaut and den Hertog, United States Patent 2,129,294 (1938).

397. Williams, Chem. and Eng. News, 21, 1148-51 (1943).

398. Williams, Proceedings of the 25th Annual Meeting of the New Jersey Mosquito Extermination Association (1938).

399P. Wolffenstein, German Patent 520,155 (1926).

400. Work, J. Chem. Soc., 1315-20 (1940).

401. Yorke, Trans. Roy. Soc. Trop. Med. and Hyg., 33, #5, 463-82 (1940).

402. Young, U. S. Pub. Health Repts., 54, 1509-11 (1939); Chem. Abs., 33, 8305 (1939).

403. Young, Hartung and Crossley, J. Am. Chem. Soc., 58, 100 (1936).

404P. Zerweck and Kunze, German Patent 615,184 (1935); British Patent 437,317 (1935); Chem. Abs., 29, 6249 (1935).

405P. Zerweck and Kunze, United States Patent 2,086,691 (1937); German Patent 615,184 (1935); British Patent 437,137 (1935).

406. Ziemann, "Malaria and Blackwater Fever," Ed. 3, Barth, Leipzig, 1924.