1946

High-molecular weight compounds of nitrogen and sulfur as therapeutic agents

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Recommended Citation
Massie, Samuel Proctor, "High-molecular weight compounds of nitrogen and sulfur as therapeutic agents " (1946). *Retrospective Theses and Dissertations*. 13173.
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HIGH-MOLECULAR WEIGHT COMPOUNDS OF NITROGEN AND SULFUR AS THERAPEUTIC AGENTS

by

Samuel Proctor Massie

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

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Dean of Graduate College

Iowa State College

1946

ACKNOWLEDGMENT

The author desires to thank Dr. Henry Gilman for his encouragement, criticism, and advice given throughout the course of this investigation.

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I. INTRODUCTION

One of the outstanding chapters in man's history has been his struggle against disease. From the earliest days man has sought to alleviate and cure his ills and pains by herbs, mineral waters, and potions, but it was late in the nineteenth century when the first synthetic drugs were made. The brilliant work of Ehrlich gave the greatest stimulus to the possibility of conquering disease by systematic synthetic chemotherapy. Ehrlich himself dreamed that there would be found a drug specific for each disease.

After the first enthusiasm arising from the success of the arsenicals and other metallic drugs had subsided, the "sulfa" drugs next gave substance to Ehrlich's dream. This remarkable group of drugs has helped in the fight against many formerly unchecked diseases and together with the notable bacterial drugs, penicillin, gramicidin, and streptomycin, bids to make man's life longer and easier.

However, there are a few diseases with which synthetic chemotherapy has had little success. Among these are malaria, tuberculosis, leprosy and cancer. Malaria seems destined to be checked, due to the control of the mosquitoes by better sanitation and the newer insecticides, and the drugs, atebrin, plasmoquin and paludrine.

In the search for newer and better chemotherapeutics, one approach seems to be lipophilic therapeuticals, i.e., drugs containing high-molecular weight aliphatic groups. The theory of lipophilic chemotherapeuticals has been outlined briefly by Bergmann and Haskelberg.[1] They state in their introductory paragraphs:--

"The systematic synthesis of substances expected to have chemotherapeutical value is based on Ehrlich's postulate that they should have affinity for the tissue forming the cell-wall of the parasite but not for that of the host. There are still a few maladies in which chemotherapeutical investigations have had but little success, e.g., tuberculosis, leprosy, and parasitic diseases of the _Theilera_ type."

"In seeking a new type of chemotherapeutical, intended to have affinity to the lipoids and not to the proteins, we were influenced by two considerations: (i) the cell-walls of tubercle and of leprosy bacilli are known to consist largely of lipoid material, so it was expected that they would exhibit a selective affinity for lipophilic substances, (ii) such substances should be effective in all cases in which the infected tissue is lipoidal in character."

The preparation of high-molecular weight therapeutic agents is of interest for several reasons. (1) Molecular structures which are now useful in drugs may become more useful, and molecular structures which show no activity may become effective if their solubility in lipoidal tissue is increased. (2) Techniques developed for their preparation may

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[1] Bergmann and Haskelberg, _J. Chem. Soc._, 1 (1939).

be useful in other types of synthesis. (3) Intermediates and the final compounds may have other chemical uses. (4) From the purely theoretical viewpoint they increase our knowledge of homology.

The difficulty of correlating the chemical structure and therapeutic value of chemotherapeutic agents has been given by Clark.[2] Homologues do not necessarily produce similar physiological action and may even be antagonistic in their action. In the preparation of lipophilic therapeuticals, therefore, it is not essential to follow the line of homology. In many cases, however, this is an advisable method.

The investigations in this thesis describe the preparation of nitrogen and sulfur compounds containing high-molecular weight aliphatic groups, from dodecyl to octadecyl, (C_{12}-C_{18}), which may be useful as therapeutic agents, especially in the treatment of malaria and tuberculosis.

The general approach has been the introduction of these high-molecular weight aliphatic groups into (a) molecular structures known to confer chemotherapeutic activity, and into (b) molecular structures not yet known to have any physiological effect, but which contain chemically active groups.

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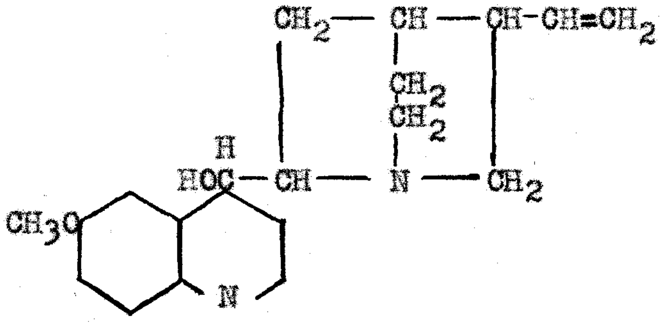
2. Clark, in Heffter, Heubner, and Schüller's "Handbuch der experimentellen Pharmakologie". Springer, Berlin (1937), Volume IV, p. 217.

II. HISTORICAL

A. Chemotherapy of Malaria

The first and one of the most successful antimalarials has been quinine (I). Since the Countess of Chinchon was cured in 1628 by the marvelous Peruvian bark, this substance has been used to combat malaria. The cinchonina bark, which contains quinine and other alkaloids was first administered as a powder. Later the pure material was extracted from the bark. However, the pure drug was so expensive that its benefits were only available to the rich. This led the French Society of Pharmacy in 1850 to offer a prize of four thousand francs for the synthetic preparation of quinine. It was many years later (in 1945) before the total synthesis of quinine was realized.[3] This synthesis is presently of little commercial value as it involves many steps to produce only a small amount of material.



(1)

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[3] Woodward and Doering, J. Am. Chem. Soc., 67, 860 (1945).

However, the contest had many good results. It stimulated much valuable research, especially on the quinoline nucleus, in the hope of preparing either quinine or a suitable substitute. One of its greatest indirect benefits was from the efforts of William Henry Perkin, which led to the beginning of the great synthetic dye industry.

In 1908 Rabe proposed the structure of quinine which is accepted today and in 1931 he synthesized dihydroquinine.[4] His work was verified by Woodward and Doering.[3]

Quinine is antischizontal,[5] and is therefore suitable in the treatment of acute malaria. The drug possesses several disadvantages. In addition to personal idiosyncrasies (hypersensitivity), quinine poisoning is not infrequent. Cinchonism may result from repeated administration of full doses. This malady is characterized by impaired hearing and vision, nausea, and headache, and may extend to serious disturbances of the gastro-intestinal and central nervous systems.

The difficulties in the synthesis of quinine led to the study of other molecules as antimalarials. Guttmann and Ehrlich showed in 1891[6] that methylene blue exhibited some anti-

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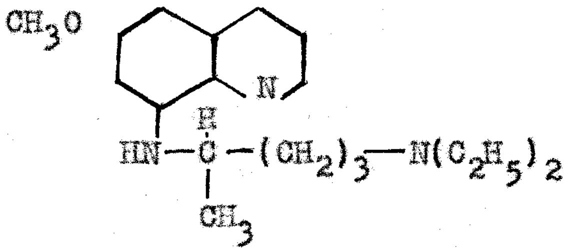
[4] Rabe and co-workers, Ber., 64B, 2487 (1931).

[5] For a general discussion of the malarial cycle, see Spatz, S.M., Doctoral Dissertation, Iowa State College, (1941).

[6] Guttmann and Ehrlich, Berlin. klin. Wochschr., 28, 593 (1891) /Chem. Zentr., I, 221 (1892)/.

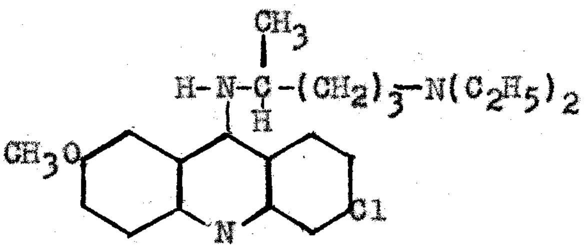
malarial activity, and later other compounds closely related to methylene blue were shown to be of therapeutic value. Years of research in an extensive systematic program at I. G. Farbenindustrie yielded plasmoquin[7] (II). Plasmoquin is one of



(II)

the most effective agents known in avian malaria. It is gametocidal[5] in action, but its use in humans is limited as the therapeutic dose often approaches the toxic dose. The most common toxic effects are cyanosis and methemoglobin formation. Cinchonism, however, is not produced.

The next good antimalarial introduced was atebrin[8] (III).



(III)

During World War II, when our supply of quinine was cut off,

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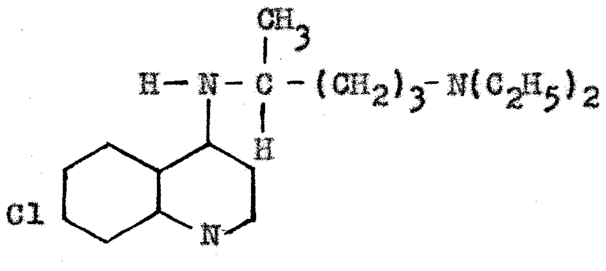
[7] Schuleman, Schönhofer, and Wingler, German Patent, 486,079. (1924) [C.A., 24, 1937 (1930)].

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

this drug was the most important antimalarial. It has been proven far superior to quinine. Atebrin, like quinine is schizontal in action, as compared with the gametocidal action of plasmoquin. As a result a combination of quinine and plasmoquin or atebrin and plasmoquin has been much used in clinical practice. The toxicity of atebrin is relatively low. Abdominal pain, headache, and gastric disturbances are occasionally noted. The skin may turn yellow, but no harm results from this coloration.

The success of plasmoquin and atebrin increased considerably the interest in synthetic antimalarials. In recent years thousands of compounds have been prepared and tested under the auspices of the Allied Governments. Since the end of World War II, there has been announced the preparation of three drugs, for which superiority over atebrin, plasmoquin, and quinine is claimed.

One of the most promising drugs appears to be SN 7618[9] or 7-chloro-4-(4'-diethylamino-1'-methylbutylamino)-quinoline (IV).



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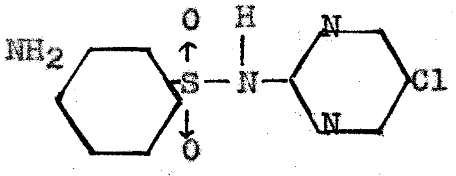
[9] This number refers to the Survey Number of the drug in the research program of the United States Government.

This drug was first synthesized by Anderson, Breitner, and Jung[10], but apparently its outstanding antimalarial properties were not noted and it remained for Surrey and Hammer[11] to prepare it and recognize its therapeutic possibilities. SN 7618 acts as an effective suppressant when given only once a week, is well tolerated, and does not color the skin. More physiological information awaits further clinical testing.

A second drug recently announced is Metachloridine,[12] 2-(*m*-aminobenzenesulfonylamino)-5-chloropyrimidine (V). A full description of its pharmacological properties, however, has not been released.



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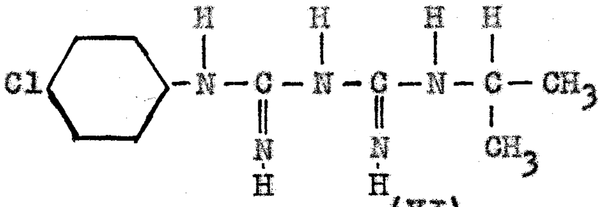
The third new antimalarial is Paludrine, N^1- *p*-chlorophenyl N^5-isopropyl biguanide[13] (VI).



(VI)

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[10] Anderson, Breitner, and Jung, German Patent, 683,692 (1939) [*C.A.*, *36*, 4973 (1942)].

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

[12] See, Volwiler and MacCorquodale, *Chem. Eng. News*, *24*, 346 (1946).

[13] Curd and Rose, *Chem. and Ind.*, 75 (1946).

This drug appears to be unique as it exhibits high prophylactic action[14] in addition to its suppressive action. Neither quinine nor atebrin possesses any true prophylactic action, that is, they do not prevent infection, but only act to control or suppress the clinical symptoms. Paludrine appears remarkably free from toxic effects and is claimed to be more active than atebrin or quinine for the treatment of clinical malaria.[15]

The last three drugs are, however, too new for a proper evaluation of their therapeutic properties. Nevertheless, they give stimulus to the hope that the "perfect" antimalarial may be found.

The vast number of compounds tested for therapeutic action in malaria has led to the formulation of many generalizations and predictions concerning chemical structure and activity.[16] Spatz[5] has prepared a rather comphrehensive review of chemical constitution and antimalarial action.

It might be well to note, however, some similarities in the structures of the better antimalarials. Four of these compounds, (I), (II), (III), (IV) are quinoline derivatives, while one of them (V) is a pyrimidine derivative. This nuc-

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14. Curd, Davey, and Rose, Ann. Trop. Med. Parasitol., 39, 208 (1945).

15. Adams and co-workers, ibid, 39, 225,232 (1945).

16. Tolman, L.L., Doctoral Dissertation, Iowa State College (1945).

leus, very important in fundamental biology because of its wide occurrence in nucleoproteins and enzymes, may be the basis of a new type of antimalarial research. This research may be founded on the possibility of discovering compounds which acting analogously to the sulphanilamide drugs may interfere with the vital processes of the malaria parasites.[13] Three of them, (I), (II), and (III), contain a methoxyl group para to the heterocyclic nitrogen. Compounds (III) and (IV) possess a chloro group in the 7- position of the quinoline nucleus whereas in (V), the chloro group is in the 5- position of the pyrimidine ring. Compounds (II), (III) and (IV) contain the same basic side-chain, $-\overset{H}{N}-CH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$, but the dialkylaminoalkylamino group is attached in a different position in (II). The basic side-chain in (I) contains a secondary carbinol group.

There still remains a great need for antimalarial agents which possess prophylactic as well as therapeutic action so as to aid man in his fight against one of his greatest enemies, malaria.

B. Chemotherapy of Tuberculosis

General

The chemotherapy of tuberculosis is a fundamentally different problem from that of diseases such as syphilis and streptococcus infections, which have been successfully treated by synthetic drugs. Most of these diseases are caused by parasites, trypanosomes and spirochetes, which have no capsule and which circulate in the blood stream unprotected. Tubercle bacilli, in contrast, are rarely found in the blood stream and have a protective waxy capsule. These bacteria are also well protected by a mass of tissue called the tubercle. In addition phagocytic cells, which usually destroy bacteria, form a wall around these germs and prevent their easy destruction. These considerations show the difficulty of direct and immediate bactericidal action.[17]

Destruction of the tubercle bacilli requires penetration of the avascular tubercle and the waxy substance by the drug. The phagocytic cell, also, must often be entered. The goal of antituberculous chemotherapy is the destruction of the bacilli found in the infected host without harming the host. The nature of the disease, however, makes difficult the task of find-

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[17] For a general discussion of the chemical basis of therapeutics in tuberculosis, see Wells and Long, "The Chemistry of Tuberculosis", Williams and Wilkins, Baltimore, Maryland, (1932). p. 391.

ing a true chemotherapeutic agent.[18]

The chemotherapeutic agents prepared for testing against tuberculosis may be divided into three groups[19]: "(a) compounds prepared by pure empiricism; (b) drugs conceived from consideration of the drug versus metabolite antagonist theory;[20] (c) compounds designed to penetrate the lipid or waxy layer of the acid-fast bacteria and so get at the protoplasm of the organism".

The results so far reported are not conclusive enough to permit any definite correlation between chemical structure and antituberculous activity. These results, however, do give information which may be valuable in further chemotherapeutic studies.

Empirical Drugs

In vitro testing of thousands of random chemicals has revealed only a few strongly tuberculocidal compounds. These active compounds include certain metallic compounds as gold thiocyanate, gold diacetyl and gold sodium thiosulfate[17] (sanocrysin) and organic mercury compounds as the *bis*-sodium

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[18] A true chemotherapeutic agent, in the sense of Ehrlich, is one which chemically disinfects the body by killing the specific disease organisms in a single non-lethal dose.

[19] Burger, *J. Chem. Ed.*, *22*, 587 (1945).

[20] Woods and Fildes, *Chemistry & Industry*, *18*, 133 (1940).

p-nitrophenolate of mercury and *p*-N-ethylaminonitrobenzene mercury acetate.[21] Alkaloids and alkaloidal drugs such as harmine, conessine, ethylapoquinine and aminohydroquinine have seemed worthy of further study.[22] Vitamins (cod-liver oils) and hormones (diethylstilbestrol) were found to be of value.[19] Aromatic ketones[23] and their halogenated derivatives[24] and basic ethers of halogenated phenols[25] have shown activity. Basic dyes[26] were tested which were supposed to be tuberculocidal because of their negative charge when suspended in serum. Two azine compounds, safranin and tannin heliotrope, appeared to exert favorable action.

Melville and Stehle[27] examined seventy compounds, mostly aniline derivatives, but found no significant results. Guaiacol and some of its derivatives as well as aromatic hydrocarbons have aided in pulmonary tuberculosis. They have given

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21. Dewitt, *Am. Rev. Tuberc.*, *8*, 234 (1923).

22. Meissner and Hesse, *Arch. exptl. Path. Pharmakol.*, *147*, 339 (1930).

23. Freedlander, (a) *Proc. Soc. Exptl. Biol. Med.*, *51*, 153 (1942); (b) *Am. Rev. Tuberc.*, *49*, 543 (1944).

24. Freedlander, *Calif. and Western Med.*, *61*, 85 (1944).

25. (a) Saz, Johnston, Burger, and Bernheim, *Am. Rev. Tuberc.*, *48*, 40 (1943); (b) Burger, Wilson, Brindley, and Bernheim, *J. Am. Chem. Soc.*, *67*, 1416 (1945).

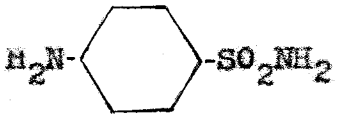
26. (a) Smith, *J. Pharmocol.*, *20*, 419 (1923); (b) Hesse, Meissner, and Quast, *Arch. exptl. Path. Pharmokol.*, *135*, 82 (1928); (c) Meissner and Hesse, *ibid*, *159*, 687 (1931).

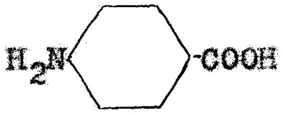
27. Melville and Stehle, *Can. J. Research*, *22E*, 95 (1944).

occasional relief but no cure. It should be strongly emphasized that, because of the varying nature of tubercular lesions, many substances have aided particular cases. None of these "empirical" drugs has been very helpful in general clinical treatment of tuberculosis.

Metabolite Antagonists

Since 1940[20] much of the planning of chemotherapeutic agents has been directed toward the preparation of compounds similar in chemical structure to the substances required by the bacteria for existence, yet antagonistic in their physiological action. According to this theory,[28] the bacteria try to substitute structurally similar sulfanilamide in their metabolism for *p*-aminobenzoic acid, an essential growth factor for many bacteria. Sulfanilamide causes bacteriostasis because it does not fulfill the growth and reproduction requirements of the bacteria. Drugs of this type do not destroy the organism, but permit the normal body defense mechanisms to complete the task. Thus, addition of more *p*-aminobenzoic acid


sulfanilamide


p-aminobenzoic acid

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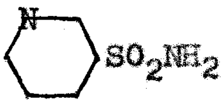
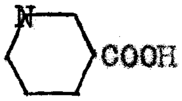
[28] (a) Woods, *Brit. J. Exptl. Path.*, *21*, 74 (1940); (b) Jenkins and Hartung, "The Chemistry of Organic Medicinal Products", John Wiley and Sons, Inc., New York, N.Y. (1943), p. 431.

reverses the effect of sulfanilamide.

3-Sulfamylpyridine causes inhibition of the growth of bacteria requiring nicotinic acid as an essential growth substance.



3-sulfamylpyridine



nicotinic acid

In the case of the tubercle bacilli only a limited number of metabolic studies have been made. These studies show that the bacteria choose a typical cell diet of nitrogenous materials and salts, their sole source of carbon being glycerol or its oxidation products such as pyruvic acid.[29] They can adapt themselves to unrelated compounds such as benzoic and salicylic acids.[30] The bacilli need oxygen for their growth. Typical antioxidants such as diphenylamine inhibit the growth of cultures.

A number of aminosubstituted aromatic sulfones whose structure classifies them as metabolite antagonists to *p*-aminobenzoic acid[31] have been tested. The most promising syn-

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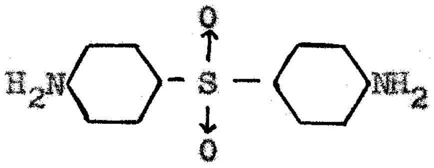
[29] Cf. Boissevain, *Proc. Soc. Exptl. Biol. Med.*, *54*, 342 (1944).

[30] Bernheim, (a) *Science*, *92*, 204 (1940); (b) *J. Bact.*, *41*, 387 (1941); (c) *J. Biol. Chem.*, *143*, 383 (1942).

[31] (a) Steenken and Heise, *Proc. Soc. Exptl. Biol. Med.*, *52*, 180 (1943); (b) Bell and Roblin, *J. Am. Chem. Soc.*, *64*, 2905 (1942).

thetic compounds have been found in this group. The parent compound of the series, 4,4'-diaminodiphenyl sulfone (VII) is used as a reference compound for *in vitro* testing.[32] In spite of high antituberculous activity the toxicity and insolubility of this compound have prevented significant clinical tests. Much research has been directed toward modification of the structure of 4,4'-diaminodiphenyl sulfone so as to increase solubility and lower toxicity.



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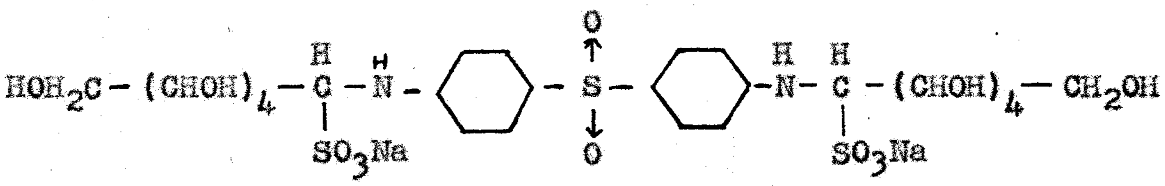
Promin,[33] its *bis* (glucose sulfonate) (VIII) and diasone,[34]



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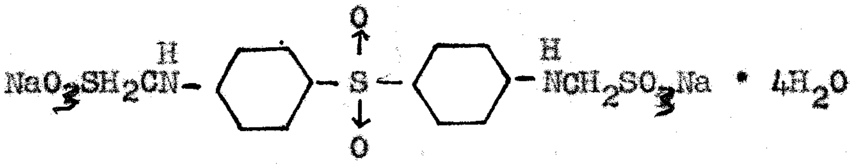

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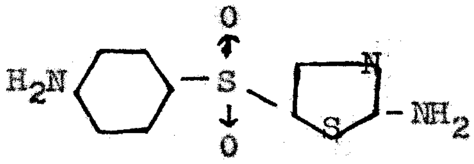
32. (a) Calloman, *Am. Rev. Tuberc.*, *47*, 97 (1943); (b) Feldman and Hinshaw, *ibid*, *51*, 582 (1945).

33. Feldman, Hinshaw, and Moses, *Proc. Staff Meetings Mayo Clinic*, *15*, 695 (1940).

its *bis* (N-methylene sodium sulfoxylate) (IX) are much more soluble and exhibit such a low toxicity that both have been subjected to extensive clinical trials.[35] However, their curative effects are too erratic to justify their general therapeutic use.

A newer agent is promizole, 4-aminophenyl-2'-aminothiazolyl-5'-sulfone[36] (X) which shows a particularly low toxicity



(X)

and a high antitubercular activity *in vivo*.[37] Preliminary clinical trials in man have been promising.

Smith, Emmart, and Westfall[38] tested twenty-three compounds, including sulfonamides, sulfones and related phosphorus compounds and concluded from their studies that the diaminodiphenyl sulfone nucleus appears to be a significant point of departure for further investigations in the field of

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34. Raiziss, *Science*, *98*, 350 (1943).

35. Hinshaw and Feldman, *Med. Clinics N. America*, *29* [*4*], 919 (1945).

36. Bambas, *J. Am. Chem. Soc.*, *67*, 671 (1945).

37. Feldman, Hinshaw, and Mann, *Am. Rev. Tuberc.*, *50*, 418 (1944).

38. Smith, Emmart, and Westfall, *J. Pharmocol.*, *74*, 163 (1942).

chemotherapy. Heymann[39] prepared a series of derivatives of 4,4'-diaminodiphenyl sulfone but tested them for antimalarial rather than antituberculous properties. Goldberg and Besly[40] prepared a series of p-aminobenzenesulfonylalkylcarboxylic acids as more soluble derivatives of 4,4'-diaminodiphenyl sulfone.

As a result of the chemotherapeutic activity of sulfanilamide and related substances in other infections, a large number of studies has been undertaken to determine the effects of this group of agents in experimental tuberculosis. Corper, Cohn, and Bower[41] have published a good review of the effects of sulfanilamide in experimental tuberculosis. Neither sulfanilamide nor its derivatives have shown any special value in the chemotherapy of tuberculosis.

Bernheim[30a] showed that salicylic and benzoic acids increase the oxygen consumption and carbon dioxide production of the tubercle bacilli, whereas the homologues, 3- and 4-hydroxybenzoic acids, were inactive. On this basis Lehmann[42] examined more than fifty derivatives of benzoic and salicylic

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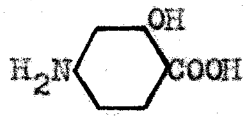
39. (a) Heymann and Fieser, J. Am. Chem. Soc., 67, 1979 (1945); (b) Heymann and Heidelberger, Ibid, 67, 1986 (1945).

40. Goldberg and Besly, J. Chem. Soc., 566 (1945).

41. Corper, Cohn, and Bower, Am. Rev. Tuberc., 40, 452 (1939).

42. Lehmann, Lancet, 250, 15 (1946).

acids as bacteriostatic agents against tubercle bacilli. *p*-Amino-salicylic acid (XI) was found active enough to justify



(XI)

its use in clinical trials, and preliminary reports are encouraging, although inconclusive.

Lipid-Soluble Agents

The planning of antituberculous agents has also been influenced by consideration of the production of lipids and waxes by the tubercle bacilli. Certain fatty acids can cause lesions or irritations similar to those produced in infections caused by acid-fast bacteria. These acids damage the bacilli in the manner of true chemotherapeutical agents.[18] This is especially true of branched fatty acids, such as tuberculostearic acid (10-methylstearic acid) and phthioic acid (ethyldecyldodecylacetic acid[43]), which were isolated by Anderson[44] from the esters produced by the bacilli. The theory has recently been advanced[45] that the inhibiting effect of branched-chained acids

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[43] Polgar and Robinson, *J. Chem. Soc.*, 615 (1943).

[44] Anderson, *Chem. Rev.*, **29**, 225 (1941).

[45] Küster and Wagner-Jauregg, *Biochem. Z.*, **317**, 256 (1944) /*C.A.*, **40**, 623 (1946)/.

is due to the replacement by these substances of the natural cellular fatty acids and the subsequent injurious effects.

Several derivatives of branched fatty acids and amines containing long forked alkyl groups were highly active against tubercle bacilli *in vitro*.[46] 1,4-Dicyclohexylbutan-2-oic acid was active in dilutions of 1:50,000. Other acids with 16 to 18 carbon atoms and some related bases in which a diethylamino group takes the place of carboxyl were tuberculocidal while homologues with 19 to 20 carbon atoms showed no activity. Chaulmoogric acid and its derivatives, very useful in leprosy, which is caused by an organism similar to the tubercle bacillus, have not proved very useful. However, they have given relief in isolated cases. Emmart[47] reports that synthetic alicyclic acids related to chaulmoogric acid seem worthy of further study.

Drea[48] in a study of antibacterial action against human tubercle bacilli in a synthetic medium found that compounds with groups of chain length C_{12}, C_{14} and C_{16} had pronounced growth-inhibiting properties. Négre and co-workers[49] discovered that the ethyl esters of dodecanoic, hexadecanoic and

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[46] Stanley, Coleman, Greer, Sacks, and Adams, *J. Pharmacol.*, *45*, 121 (1932).

[47] Emmart, *Am. Rev. Tuberc.*, *53*, 83 (1946).

[48] Drea, *J. Bact.*, *48*, 547 (1944).

[49] Négre, Berthelot, and Bretey, *compt. rend. soc. biol.*, *123*, 864 (1936); *compt. rend.*, *204*, 1372 (1937); *Rev. tuberc.*, [*5*], *4*, 344-8 (1938) [C.A., 32, 8003 (1938)].

octadecanoic acids retarded growth of bacilli in experimental tuberculosis, and Drea[50] found that sodium oleate exhibited an inhibitory effect on the growth of tubercle bacilli. Sodium tetradecyl sulfate has been found quite promising in the treatment of tubercular empyemas.[51]

N'-Dodecanoyl sulfanilamide[52] has been reported to exert a favorable effect on the course of experimental tuberculosis in guinea pigs, but Steinbach and Duca[53] could not confirm this claim.

Introduction of long-chained aliphatic groups into pyridyl sulfanilamides, however, did not give rise to activity.[54] Jensen and Kjäer[55] prepared a series of 4-alkylsulfathiazoles for testing, but no report of their pharmacological results is available. Neither 4,4'-distearoyldiaminodiphenyl sulfone nor 4,4'-dichaulmoogryldiaminodiphenyl sulfone showed any activity.[56] Lipophilic N^4-acyl derivatives of 2-(p-aminophenylsulfamido)pyridine were inactive against tubercle bacilli.[57]

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[50] Drea, J. Bact., 44, 149 (1942).

[51] Petroff, Herman, and Palitz, Am. Rev. Tuberc., 44, 738 (1941).

[52] Climeko, Proc. Soc. Exptl. Biol. Med., 43, 624 (1940).

[53] Steinbach and Duca, ibid, 44, 133 (1940).

[54] Spring and Young, J. Chem. Soc., 248 (1944).

[55] Jensen and Kjäer, Dansk Tids. Farm., 16, 116 (1942) /C.A., 38, 2326 (1944)/.

[56] Lloyd and Middlebrook, Am. Rev. Tuberc., 49, 539 (1944).

[57] Cavallini and Carissimi, Chimica e Industria (Italy), 24, 201 (1942) /Chem. Zentr. I, 1370 (1943)/.

Testings of Drugs

In vitro evaluation of antituberculous drugs, however, is not too reliable.[18,27] For example, 2,3,5-triiodobenzoic acid shows high activity *in vitro*, but *in vivo* this drug has no therapeutic activity.[58] A rapid and economical animal test is urgently needed.[34] The screening test of Feldman and Hinshaw,[32b] while thoroughly desirable pharmacologically, requires too large an expenditure of time and drug. The other tests[59] need further improvement. However, large numbers of potential antituberculous agents may be rapidly screened by these methods with some degree of reliability.

Another limitation is that drugs such as promin, 4,4'-diaminodiphenyl sulfone and the gold compounds, which are very good in experimental animal tuberculosis, may be too toxic or of too low tolerance to be valuable in human treatment.

Summary

Of the many thousands of synthetic drugs tested against tuberculosis, only three have reached extensive clinical trials,

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[58] Saz and Bernheim, *J. Pharmacol.*, *73*, 78 (1941).

[59] (a) *Omental weight test*: ref. 25a; (b) *Ocular tuberculosis test*: Steenken, Wolinsky, and Herse, *Am. Rev. Tuberc.*, *53*, 179 (1946); (c) *Chick embryo test*: Emmart and Smith, *ibid*, *47*, 426 (1943); Moore, *Am. J. Path.*, *18*, 827 (1942); (d) *Piscine infection test*: Feinstone, *Am. Rev. Tuberc.*, *46*, 101 (1942).

promin (VIII), diasone (IX) and promizole (X). A fourth compound, p-aminosalicylic acid (XI), has had preliminary clinical testing. None, however, has shown any unusual therapeutic value.

The drugs in group two (metabolite antagonists) do not kill the bacteria. They merely surpress their growth. The drugs in group three (lipid-soluble agents) offer the best hope of destroying the bacteria.

Two mold products, strepthothricin and streptomycin, seem quite promising in their treatment of tuberculosis.

Diasone and promin are derivatives of 4,4'-diaminodiphenyl sulfone and promizole has a 4-aminophenyl sulfone nucleus attached to a thiazole system. All of these compounds contain nitrogen and sulfur. The study of nitrogen and sulfur containing organic compounds, therefore, seems quite significant. Although introduction of lipophilic residues has not proved very valuable so far, the fact can not be overlooked that the solubility of these compounds may have limited their testing. One of the difficulties in testing long-chained aliphatic derivatives, as pointed out by Hoyt,[60] is the lack of a method which gives comparable results for both soluble and insoluble homologues.

The preparation of high-molecular weight compounds containing nitrogen and sulfur as therapeutic agents in tuber-

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60. Hoyt, F.W., Doctoral Dissertation, Iowa State College (1940).

culosis, therefore, seems worthy of further study.

C. High-Molecular Weight Aliphatic Compounds in Chemotherapy

Studies on the physiological effects of compounds containing high-molecular weight aliphatic groups have increased in recent years as technical advances have made available reasonably large amounts of pure starting materials. These studies have also been stimulated by the discovery that metabolic products of many forms of plant and animal life contain these groups.

Acids

Chaulmoogric acid, an unsaturated acid of the cyclopentane series containing a straight chain with 13 carbon atoms, and hydnocarpic acid, an unsaturated acid of the cyclopentane series containing 11 carbon atoms in the chain, have been found very useful in leprosy chemotherapy. On this basis Adams and co-workers[46] prepared a large series of cycloalkanecarboxylic acids and tested them against the leprosy bacilli. They found that bactericidal activity appeared to be very strongly related to surface tension lowering ability,[61] a fact later well established.[62] Their data indicated that a bac-

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[61] Stanley and Adams, J. Am. Chem. Soc., 54, 1549 (1932).

[62] Hoggerheide, J. Bact., 49, 277 (1945).

tericidally effective acid must be a good surface tension depressant and must also have a molecular weight of approximately 256, that is, one which corresponds to an acid of sixteen carbons. Hexadecanoic acid, however, had little effect, thus showing that the position of the carboxyl group is also important. Shifting the carboxyl group from atom 1 to atom 2 lowered the surface tension and increased the bactericidal action, and as the carboxyl group approached the center, these effects increased.

On this basis Hill and Fager[63] prepared a series of $\underline{\alpha}$-alkyl mercapto aliphatic acids, RSCR'COOH, where R and R' were both high-molecular weight groups. Pharmacological reports on these compounds were not given. Brady and Bogert[64] replaced the cyclopentyl nucleus in hydnocarpic acid by pyridine and thiazole for testing in rat leprosy. Their therapeutic effects are not available.

Drea,[48] in a study of the antibacterial properties of saturated fatty acids against tubercle bacilli, found that activity was most pronounced with tetradecanoic (C_{14}) and hexadecanoic (C_{16}) acids. Octadecanoic (C_{18}) acid was definitely inhibitory and dodecanoic (C_{12}) acid slightly less inhibitory. The acids with one to five carbon atoms had little or no growth preventing effects, while the acids from C_6 to C_{12}

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[63] Hill and Fager, J. Am. Chem. Soc., 65, 2300 (1943).

[64] Brady and Bogert, ibid, 65, 1075, 1081 (1943).

showed less activity than the higher homologues.

Metabolic studies on the feeding of sebacic, decane-, tetradecane- and hexadecanedioic acids as disodium salts to dogs and the last three to man showed that utilization in the body increased with chain length.[65] α-Mercapto and α-disulfido fatty acids of high-molecular weight have germicidal properties which suggests their use as germicidal soaps.[66] No significant antimalarial activity has been shown by high-molecular weight aliphatic fatty acids.

Esters

The ethyl esters of the branched acids prepared by Adams and co-workers showed no activity against leprosy bacilli; this was attributed to their inability to lower surface tension.[61] Mention has been made of the retarding action of the ethyl esters of dodecanoic, hexadecanoic and octadecanoic acids in experimental tuberculosis in guinea pigs.[49]

Long-chained esters of pyridinecarboxylic acids showed no value as local anesthetics.[67] p-Alkoxybenzoates of secondary amino alcohols (XII) have been found to be good anesthetics,

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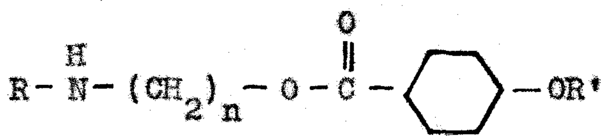
[65] Emmrich and Emmrich-Glaser, Z. physiol. Chem., 266, 183 (1940).

[66] Eggerth, J. Exptl. Med., 53, 27 (1931).

[67] Blicke and Jenner, J. Am. Chem. Soc., 64, 1721 (1942).



(XII)

but if n is larger than six the effect drops.[68]

Amides

D'Alelio and Reid[69] prepared N-methyl amides of aliphatic acids from formic to stearic and found the eight-, nine- and ten-carboned members to possess local anesthetic properties. The toxicity increased with chain length. N-*n*-Dodecyl acetamide has been reported useful medicinally.[70]

Buck and co-workers[71] investigated the pharmacological action of alkylureas and isoureas from methyl to *n*-docosylurea (C_{22}). They discovered that these compounds had anesthetic effects and toxicities which increased with chain length.

Amines

Fuller,[72] using 20 different strains of bacteria, reported that the antibacterial activity of straight-chained ω-mono

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68. Pierce, Salsbury, and Fredricksen, U.S. Patent, 2,372,116 (1945) [*C.A.*, *39*, 3630 (1945)].

69. D'Alelio and Reid, *J. Am. Chem. Soc.*, *59*, 109 (1937).

70. English patent, 458,454 (1937) [*Chem. Zentr.*, I, 2867 (1937)].

71. deBeer, Buck, and Hjort, *J. Pharmacol.*, *52*, 216 (1934).

72. Fuller, *Biochem. J.*, *36*, 548 (1942).

and diamines, amidines, guanidines and quaternary bases in broth increased with chain length up to a maximum, then decreased. This maximum depended on the strain of bacteria used. The activity for the mono-substituted compounds increased up to the C_{12}-C_{16} chains.

King, Laurie, and Yorke[73] found long-chained amidines to be effective against trypanosomes.

Heptadecylamine hydrochloride was toxic to frogs, dogs and guinea pigs.[74] Valko and DuBois,[75] examining a series of primary and tertiary amine hydrochlorides from decyl to octadecyl with the corresponding dimethyl derivatives against Staph. aureus and E. typhi, reported dodecylamine hydrochloride to be the most effective agent. Noteworthy is the fact that 9-octadecenyl-(oleyl)-amine was over three times as active as the saturated octadecylamine.

In tests of toxicity to the housefly, Dahm and Kearns[76] found that straight-chained alkyl secondary amines, with identical alkyl groups or groupings differing by one CH_2 group, were more toxic than isomers in which the alkyl groups differed by more than one CH_2 group. Branched-chained alkyl groups lowered the toxicity. N-Hexyl-N-heptylamine showed the

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[73] King, Laurie, and Yorke, Lancet, 233, 1360 (1937).

[74] Flaschenträger and Lachmann, Z. physiol. Chem., 192, 268 (1930).

[75] Valko and DuBois, J. Bact., 50, 489 (1945).

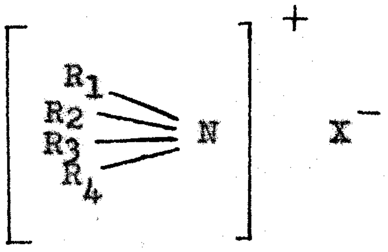
[76] Dahm and Kearns, J. Econ. Entomol., 34, 462 (1941).

greatest speed of action. Ralston and Barrett[77] found dioctylamine to be the most active of a series of secondary amines examined against the house fly. The activities of methyldodecylamine and didodecylamine were much lower.

Quaternary Ammonium Derivatives

The reaction of hexamethylenetetramine with a large variety of substituted benzyl or alkyl halides to form quaternary ammonium salts with pronounced bactericidal properties was announced by Jacobs and co-workers in 1916.[78] Unfortunately little attention was given to these observations.

Domagk[79] in 1935 again noticed the physiological activity of this group of compounds. This worker observed that bactericidal properties are not limited to the quaternary salts of hexamethylenetetramine. They are a general property of a large number of quaternary ammonium salts having the general formula:



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[77] Ralston and Barrett, <u>Oil and Soap</u>, <u>18</u>, 11 (1941).

[78] Jacobs and co-workers, <u>J. Exptl. Med.</u>, <u>23</u>, 569 (1916). Dr. Jacobs in a preceding paper, <u>ibid</u>, <u>23</u>, 563 (1916) gives an excellent discussion, still valid, on chemotherapeutic agents in bacterial infections.

[79] Domagk, <u>Deut. med. wochschr.</u>, <u>61</u>, 829 (1935).

According to Domagk, all compounds in which at least one radical, R_1 is a long-chained aliphatic group (C_8H_{17} to $C_{18}H_{37}$), either straight- or branched-chained groups, possess this activity. The other three radicals (R_2, R_3, R_4) may be either one, two or three lower alkyl radicals. Benzyl or other aliphatically bound phenyl radicals may also be used. Two or three of them can even be arranged to form a cyclic compound as in the case of quaternary salts of pyridine, piperidine or morpholine. The radical X is either a halide or a group such as sulphate or acetate. These compounds are also known as "invert soaps".

A wide variety of compounds, all within the broad field outlined by Domagk, has been synthesized since his studies were made. Many of them have been studied in great detail.[80,81] They find widespread use at present as antiseptics for surgical and gynecological procedures, such as skin and wound disinfection, and for sterilization of surgical instruments.

These studies have shown that the $C_{16}H_{33}$ radical appears to confer maximum germicidal action.[82] Cetylpyridinium chlor-

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[80] For excellent reviews on quaternary ammonium salts see: (a) ref. 62; (b) ref. 75; (c) Rawlins, Sweet, and Joslyn, J. Am. Pharm. Assoc., 32, 11 (1943).

[81] For studies on high-molecular weight alkyldimethylbenzylammonium chlorides, see: Dunn, Proc. Soc. Exptl. Biol. Med., 35, 427 (1936); Am. J. Hyg., 26, 46 (1937); Am. J. Surg., 41, 268 (1938).

[82] Shelton and co-workers, Proc. Am. Chem. Soc., Sept. 1939, April, 1940.

ide[83] is one of the most potent bactericidal agents known at present. Its bactericidal action *in vitro* is far greater than that of the common antiseptics such as iodine, phenol and mercurial compounds and even better than some of the recently isolated antibiotics.[62] This drug has more activity than merthiolate or hexylresorcinol against *Streptococcus hemolyticus* in mice.[84] Cetyltrimethylammonium bromide (CTAB)[64] has also found widespread use as a skin disinfectant,[85] an antiseptic medium for gloveless surgery[86] and as an agent in the treatment of impetigo, a skin disease especially prevalent in children.[87]

The activity of these compounds, as in the case of the acids,[61] seems related to their surface-tension lowering ability.[62]

No information is available on the value of these compounds as therapeutic agents in malaria or tuberculosis. It should be mentioned that many of the successful agents in chem-

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[83] (a) Blubaugh and co-workers, *J. Bact.*, *39*, 51 (1940); *ibid*, *41*, 34 (1941); (b) Warren, Becker, Marsh, and Shelton, *J. Pharmacol.*, *74*, 401 (1942); (c) Huyck, *Am. J. Pharm.*, *116*, 50 (1944).

[84] Sarber, *J. Pharmacol.*, *75*, 277 (1942).

[85] Barnes, *Lancet*, *242*, 531 (1942).

[86] Williams, Clayton, Duncan, and Miles, *ibid*, *244*, 522 (1943).

[87] (a) Forman, *ibid*, *245*, 174 (1943); (b) Fischer, *Arch. Pediatrics*, *61*, 352 (1944).

otherapy are amine derivatives. These compounds are frequently administered as their quaternary ammonium salts.

Miscellaneous Aliphatic Nitrogen Compounds

Ruzicka[88] prepared a series of polymethyleneimines from pentadecamethyleneimine to octadecamethyleneimine and found that the fifteen-carboned member had strong persistent anesthetic action. This effect was still evident to a slighter extent with the sixteen-carboned member, but disappeared in the seventeen- and eighteen-carboned members.

Because of the value of amyl nitrite in heart disease, Krantz and co-workers[89] tested the pharmacological properties of dodecyl, undecyl, tetradecyl, hexadecyl and octadecyl nitrites. These were found to have little or no effect when inhaled due to their low vapor-pressure. However, when dissolved in an alcoholic solvent and injected intravenously, they elicited full depressor responses.

Alcohols and Phenols

Asano and Yamaguti[90] synthesized 2-tetradecyl-3,6-dihy-

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88. Ruzicka, Saloman, and Meyer, Helv. Chim. Acta., 20, 109 (1937).

89. Krantz, Carr, and Forman, Proc. Soc. Exptl. Biol. Med., 42, 472 (1939).

90. Asano and Yamaguti, J. Pharm. Soc. Japan, 60, 585-91 (abstracts in English) 273, 42 (1940) /C.A., 36, 81 (1942)/.

droxyquinone and found it to be identical with rapanone, an anti-helminitic compound. These workers also synthesized other long-chained quinones but gave no report of their physiological activity. Niemann and Wagner[91] synthesized high-molecular weight glycols and report them to be of physiological interest.

3-_n_-Pentadecylcatechol (hydrourushiol) has been identified as the allergenic principle of poison ivy. This compound is recommended as the stable crystalline standard allergen for future testing in poison ivy chemotherapy.[92] Backer and Haack,[93] studying the fruit of _Anacordium occidentale_ Linn., found a vesicant acid which they named anacardic acid and identified as 2-hydroxy-6-pentadecadienyl benzoic acid. These workers also prepared 2,3-dihydroxyheptadecenylbenzene (glutarenghol) which had vesicant activity.

The high-molecular weight alcohols have not proved to be very effective as anesthetics.[94]

The color reactions of α- and β-leprosol obtained from the leprosy bacilli seemed to indicate that these compounds might be trialkyl resorcinols. Butenandt and Stodola[95] pre-

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91. Niemann and Wagner, _J. Org. Chem._, _7_, 227-32 (1942).

92. Mason, _J. Am. Chem. Soc._, _67_, 1539 (1945).

93. Backer and Haack, _Rec. trav. chim._, _60_, 66 (1941).

94. Macht and Davis, _Proc. Soc. Exptl. Biol. Med._, _30_, 1294 (1933).

95. Butenandt and Stodola, _Ann._, _539_, 40 (1939).

pared a series of long-chained resorcinols for comparison but reported no pharmacological properties.

No significant effect of long-chained alcohols and phenols in malaria and tuberculosis has been reported.

Aliphatic Sulfur Derivatives

Baker, Harrison, and Miller,[96] using Staph. aureus, Sarcona lutea and E. coli in their studies of straight-chained alkyl sulfates and sulfoacetates, found that the C_{12}, C_{14} and C_{16} compounds were the most effective for metabolic inhibition. Secondary long-chained alkyl sulfates also were shown to be good germicides.[97]

Metallic Derivatives

Metallic compounds containing long-chained aliphatic groups have not been much used in chemotherapy. Meals[98] has given a good review of long-chained organometallic derivatives. He prepared several series of compounds, but no results were given as to their pharmacological activity. Kharasch[99] pre-

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[96] Baker, Harrison, and Miller, J. Exptl. Med., 73, 249 (1941).

[97] Baker and Miller, U.S. Patent, 2,380,001 (1945) [C.A., 39, 4200 (1945)].

[98] Meals, R.N., Doctoral Dissertation, Iowa State College (1941).

[99] Kharasch, U.S. Patent, 2,129,376 [Chem. Zentr., I, 1803 (1939)].

pared a series of high-molecular weight amine salts with merthiolate for use as bactericides and fungicides, and Anigstein found bismuth butylthiolaurate to be very promising in the treatment of treponemas in the rabbit.[100]

Aromatic and Heterocyclic Derivatives

The high bactericidal action of derivatives of certain aromatic and heterocyclic nuclei has stimulated research toward the introduction of high-molecular weight aliphatic groups into these nuclei.

The use of N^1-acyl derivatives of sulfanilamide has already been given.[52,53] These derivatives have also been tested against streptococci infections in mice.[101] N^1-Dodecanoylsulfanilamide was found to be slightly superior to sulfanilamide, but as a class the long-chained compounds were inferior to sulfanilamide. The lack of activity of long-chained pyridine sulfanilamides[54] and N^4-acyl derivatives of 2-(p-aminophenylsulfonamido)-pyridine[57] against tubercle bacilli has been given.

The introduction of long-chained aliphatic residues into sulfathiazole has been mentioned.[55] Long-chained benzoxazoles

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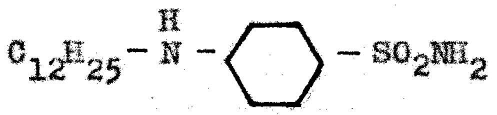
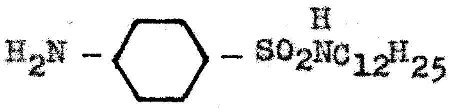
[100] Anigstein, Ann. maladies vénériennes, 32, 544 (1937); Ann. dermatol. syphil., 8, 963 (1937) /C.A., 32, 3024 (1938)/.

[101] Crossley, Northey, and Hultquist, J. Am. Chem. Soc., 62, 532 (1940).

have been found useful as synthetic anti-convulsants.[102]

Arnold and co-workers[103] prepared isomeric long-chained acyl sulfonamides. Toward pneumococcus N^4-chaulmoogroylsulfanilamide and N^4-hendecanoylsulfanilamide were inactive, N^4-hendecenoylsulfanilamide[104] was somewhat active, N^4-dodecanoylsulfanilamide was as active as sulfanilamide, whereas N^1-dodecanoylsulfanilamide was less active. 2-Aminobenzothiazole-6-sulfonamide and its 6-acetyl derivative had little therapeutic action against pneumococcus infections, whereas 2-dodecanoylamino- and 2-chaulmoogrylaminobenzothiazo-6-sulfonamides were noticeably active. N^1-Dodecanoylsulfanilamide was inactive against tuberculosis in guinea pigs.[105] N^4-Dodecanoyl-, N^1-dodecanoyl-, N^1-oleyl- and N^1-hydnocarpylsulfanilamides were inactive against rat leprosy, whereas hydnocarpylsulfonamide was slightly active.


N^4-dodecanoyl sulfanilamide


N^1-dodecanoyl sulfanilamide

Bergman and Haskelberg[1] prepared lipophilic derivatives of quinine, azo dyes, arsenicals, quinoline and acridine.

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[102] Bywater, Coleman, Kamm, and Merritt, *ibid*, *67*, 905 (1945).

[103] Arnold and co-workers, *Ber.*, *75*, 369 (1942).

[104] Cf. ref. 75. The double bond seems to exert favorable bactericidal influence.

[105] Cf. ref. 52.

They found 4-hexadecylaminoazobenzene-4'-arsonic acid to be surprisingly non-toxic to mice. Adler, Haskelberg, and Bergmann,[106] testing a series of 4-alkylaminoazobenzene-4'-arsonic acids against trypanosomes, reported the octadecyl derivative to be slightly effective. Toxicity decreased with increasing chain length.

Arnold[107] prepared a series of high-molecular weight 2-amino-1,3,4-thiodiazoles and their sulfanilamide derivatives for testing against tubercle and leprosy bacilli, but pharmacological results are not available.

One of the compounds prepared by Goldberg and Besly[40] was *p*-aminophenyl hexadecyl sulfone, but no report of its antitubercular activity was given.

Knight and Shaw[108] prepared a series of long-chained alkyl pyridines but gave no pharmacological results. Sharp[109] synthesized a series of long-chained derivatives of 2-aminopyridines for pharmacological testing but no results are available.

Arnold[110] found chaulmoogryl and oleyl thiocyanates to be effective in rat leprosy. Several *p*-thiocyanoanilines were

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[106] Adler, Haskelberg, and Bergmann, *J. Chem. Soc.*, 576 (1940).

[107] Arnold, *Ber.*, *75*, 87 (1942).

[108] Knight and Shaw, *J. Chem. Soc.*, 682 (1938).

[109] Sharp, *ibid*, 1855 (1939).

[110] Arnold, *Arch. Pharm.*, *279*, 181 (1941).

prepared. N-Oleyl-*p*-thiocyanoaniline and N-hexadecyl-*p*-thiocyanoaniline were inactive in rat leprosy. 2-Chaulmoogrylamino-6-sulfamylbenzothiazole was inactive against pneumococcus in mice.

Rajagopalan[111] prepared lipophilic derivatives of sulfanilamide, sulfathiazole, sulfathiazoline, sulfanilylsulfanilamide and sulfapyridine but gave no physiological properties. Albert, Goldacre, and Heymann[112] made 9-dodecylaminoacridine and 9-hexadecylaminoacridine, but gave no therapeutic results.

A theory has been advanced that carcinogenic substances may be "denatured"(made less active) by changing their hydrophilic properties to hydrophobic properties.[113] As a beginning in the study of this question, several long-chained flavins were prepared, but complete physiological results were not given.

Neither replacement of the *N*-ethyl groups in the diethylaminoalkylamino side-chains by larger aliphatic groups in the better antimalarials nor lengthening the alkyl groups between the amine nitrogens in the basic side-chains has been too promising. Glen and Robinson,[114] in a study of α-ω-diamino-6-methoxyquinolines, found the meconate of 8-β-(11-diethyl-

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[111] Rajagopalan, *Current Science*, *11*, 394 (1942); *Proc. Indian Acad. Sci.*, *18A*, 104 (1943) [*C.A.*, *38*, 1217 (1944)].

[112] Albert, Goldacre, and Heymann, *J. Chem. Soc.*, 651 (1943).

[113] Lettré and Fernholz, *Ber.*, *73*, 436 (1940).

[114] Glen and Robinson, *J. Chem. Soc.*, 576 (1940).

aminohendecylamino)-propyl-7amino-6-methoxyquinoline to be active. Shirley[115] synthesized 10-octadecylphenothiazine but found it inactive in malaria.

Miscellaneous Compounds

Jerchel[116] in a continuation of studies on "invert soaps" replaced the central nitrogen atom with phosphorus and arsenic. The phosphorus and arsenic derivatives were similar in activity against Staph. aureus and were slightly better than the corresponding nitrogen derivatives.

1-*n*-Alkyl-5-ethyl-5-isobutylbarbituric acids in which the alkyl group was varied from *n*-amyl (C_5) to *n*-docosyl (C_{22}) have been investigated.[117] Low solubility prevented significant testing above C_{10} but for the lower compounds the minimum hypnotic dose was fatal in all cases.

Richardson and Reid[118] studied some α-ω-di-*p*-hydroxyphenyl alkanes having two, three, four, five, six and ten methylene groups between the phenyl groups. The lower members of the group had decided bactericidal properties, but low solubilities, especially in the higher members, made extensive testing impossible.

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115. Shirley, D.A., Doctoral Dissertation, Iowa State College (1943).

116. Jerchel, Ber., 76, 600 (1943).

117. Buck, Hjort, Ide, and deBeer, J. Am. Chem. Soc., 60, 461 (1938).

118. Richardson and Reid, ibid, 62, 413 (1940).

D. Previous Work Along Lines Studied in These Investigations

1. High-Molecular Weight Nitrogen Compounds

Tertiary Amines

Harber[119] has reviewed the methods of preparation of tertiary amines. The principal methods involve the reaction of ammonia or primary or secondary amines with alkylating agents such as halides, sulfates, *p*-toluenesulfonates or phosphates. Alkyl halides have been the most widely used alkylating agents, but their reactivity often leads to unresolvable mixtures. A modification of the alkylation with halides involving the reaction of metallic derivatives of amines with the desired halide has recently been described.[120] This method, however, sometimes leads to molecular rearrangements.[121]

Robinson and Robinson[122] found that cleavage of dialkylaminomethyl ethers with Grignard reagents gave rise to tertiary amines. Haubein[123] extended this cleavage to other organometallic compounds, especially organolithium compounds.

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[119] Harber, W.I., Doctoral Dissertation, Iowa State College (1940).

[120] Gilman, Kyle, and Benkeser, *J. Am. Chem. Soc.*, *68*, 143 (1946).

[121] The phenomenon is discussed in the next section of this thesis.

[122] Robinson and Robinson, *J. Chem. Soc.*, *123*, 532 (1923).

[123] Haubein, A.H., Doctoral Dissertation, Iowa State College (1942).

Tertiary Amines from Molecular Rearrangements

It was observed in the preparation of some amino-derivatives of dibenzofuran that reaction of a halide in which the halogen was ortho to the ether linkage with sodamide in liquid ammonia gave the meta amino-derivative.[124] Extension of this work showed the rearrangements occurred with other ether[124] and sulfide[125] linkages. The use of dialkyllithium amides in place of sodamide in ether solution gave meta tertiary amines.[126] Lithium diethylamide reacted with α-halogeno-naphthalenes to give β-diethylaminonaphthalene.[127] The yields decreased in the order of F > Cl > Br. Urner and Bergstrom[128] observed a similar rearrangement with α-chloro and α-bromonaphthalenes and potassium amide, but not with α-fluoronaphthalene. These results demonstrated that rearrangements with alkali amide types are not limited to aryl halides in which the halogen is ortho to an oxygen or sulfur linkage. Subsequent studies[120] showed that halogens ortho to dialkylamino groups underwent rearrangement.

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124. Gilman and Avakian, J. Am. Chem. Soc., 67, 349 (1945).

125. Gilman and Nobis, ibid, 67, 1479 (1945).

126. Kyle, R.H., M. S. Thesis, Iowa State College (1945).

127. Gilman, Crounse, Massie, Benkeser, and Spatz, J. Am. Chem. Soc., 67, 2106 (1945).

128. Urner and Bergstrom, ibid, 67, 2108 (1945).

Derivatives of Amines

Few derivatives of tetradecylamine or hexadecylamine are found in the literature. Adam and Dyer[129] prepared hexadecylacetamide but gave no melting point. Teunissen,[130] in a study on hexadecylamine, prepared 2,4-dinitrophenylhexadecylamine, 2,4-dinitronaphthyl-1-hexadecylamine and 1,6,8-trinitronaphthyl-2-hexadecylamine as derivatives of hexadecylamine. These reactions, however, were run in a sealed tube and did not seem to be good derivatizing reactions.

Ureas of tetradecylamine and hexadecylamine have been prepared using nitrourea.[117] Hexadecyl p-toluenesulfonamide has been mentioned in the patent literature.[131] The chloroacetamide of tetradecylamine was also mentioned in the patent literature, but no physical constants nor methods of preparation were given.[132]

Arnold and co-workers,[133] in a study of the reaction of high-molecular weight amines with carbon disulfide, prepared dihexadecylthiourea. Surprisingly enough, neither the iso-

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129. Adam and Dyer, J. Chem. Soc., 127, 73 (1925).

130. Teunissen, Rec. trav. chim., 46, 208 (1927).

131. Schroeter, German Patent, 634,687 (1936) /Chem. Zentr., II, 3947 (1936)/.

132. French Patent, 735,647 (1933) /Chem. Zentr., I, 1224 (1933)/.

133. Arnold and co-workers, Ber., 74, 1372 (1941).

cyanates, isothiocyanates nor the aromatic sulfonyl chlorides have been used to derivatize tetradecyl- and hexadecylamines.

2. High-Molecular Weight Sulfur Compounds

Quinoline Sulfides

No quinoline sulfides containing long-chained aliphatic groups have been described in the literature. The general method for the preparation of the lower alkyl or aromatic quinoline sulfides involves the reaction of an active halogenoquinoline with the sodium salt of the mercaptan or thiophenol or the reaction of the sodium salt of the quinoline mercaptan with an active halide.

Hydroxy Sulfides

Secondary hydroxy sulfides have been prepared by the reaction of α-bromoketones with mercaptans followed by the reduction of the ketone to the secondary alcohol.[134] The reaction of mercaptans with epoxides has not been extensively studied with epoxides above ethylene oxide. It is well known that mercaptans and ethylene oxide give mercapto alcohols,[135] and excess ethylene oxide gives rise to alcohols of the type

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134. Prelog, Hahn, Brauchli, and Beyerman, Helv. Chim. Acta., 27, 1209 (1944) [C.A., 40, 848 (1946)].

135. Nenitzescu and Scarlatescu, Ber., 68, 587 (1935).

$R'-S-CH_2CH_2-(OCH_2CH_2)_n-OCH_2CH_2OH$, when n + 1 equals the number of excess moles of ethylene oxide.[136] Epichlorohydrin and mercaptans form compounds of the type $R-S-CH_2CHOHCH_2Cl$; however, the alkali mercaptides and epichlorohydrin at low temperatures gave the mercapto epoxide.[135,137] This reaction has also been extended to cyclohexene oxide.

Imidosulfides

Imidosulfides have been prepared by the reaction of mercaptans and thiophenols with nitriles in the presence of dry hydrogen chloride.[138]

Thioketones

The extreme ease of polymerization and very disagreeable odors of thioketones containing aliphatic groups has limited the study of these compounds. The chief methods of preparation are (a) the reactions of ketones with hydrogen sulfide; (b) the reaction of methylene halides and metal sulfides; (c) the reaction of ketones and phosphorus pentasulfide.[139]

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136. English Patent, 437,590 (1934) /Chem. Zentr., I, 3019 (1936)/.

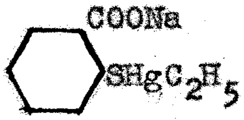
137. Gilman and Woods, J. Am. Chem. Soc., 67, 1864 (1945).

138. (a) Pinner and Klein, Ber., 11, 762 (1878); (b) Autenrieth and Bruning, ibid, 36, 3464 (1903); (c) Condo, Hinkel, Fassero, and Shriner, J. Am. Chem. Soc., 59, 230 (1937).

139. Cf. Gilman, "Organic Chemistry", John Wiley and Sons, Inc., New York, N.Y., (1944), Vol. I. p. 924.

Mercurials

Few organic mercury compounds containing sulfur have been described in the literature.[99,140,141] The best known of these derivatives is merthiolate (XIII), the sodium salt of *o*-ethylmercurimercaptobenzoic acid. This compound was first prepared by Vieth[140] in a study of the reaction of organic mercury compounds with mercaptans. It has proved to be one of the better germicides.[142]



(XIII)

Merthiolate has also proved to be very good against tubercle bacilli *in vitro*,[48] but clinical use has not been promising.[143]

3. Miscellaneous Compounds

Cinchoninic Acids

The chief methods of preparation of cinchoninic acids are

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[140] Vieth, German Patent, 399,904 (1925) [*Chem. Zentr.*, *I*, 298 (1925)].

[141] Rumpf, *Bull. soc. chim.*, *9*, 661 (1942) [*C.A.*, *38*, 2951 (1944)].

[142] Powell and Jamison, *Am. J. Hyg.*, *13*, 296-310 (1931).

[143] (a) Cummins, *Lancet*, *233*, 962 (1937); (b) Mallick, Ali, and Singh, *Tubercle*, *19*, 62 (1937) [*C.A.*, *32*, 2618 (1938)].

the Doebner-v. Miller synthesis[144] and the Pfitzinger synthesis.[145] The Doebner-v. Miller synthesis consists of the reaction of an amine, an aldehyde and pyruvic acid. The anil derived from the amine and the aldehyde may also be used with pyruvic acid. This method has the disadvantage that one-half of the amine or anil is used for the oxidation of the dihydro-acid formed from the other half.

The Pfitzinger synthesis involves the reaction of isatin or its derivatives with methyl ketones in basic solution. This method generally gives good results if the desired isatin is available, but the difficulty of synthesis of these isatins is often a limiting factor.[146]

Phenothiazine Derivatives

The chemistry of phenothiazine has been given by Shirley[115] and Van Ess.[147] Most of the research has been concerned with substitution of the hydrogen on the nitrogen, and very little study has been directed toward substitution in the ring. Scholl and Seer[148] prepared the mono- and di-phthaloyl deriva-

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[144] Doebner and v. Miller, Ber., 14, 2812 (1881).

[145] (a) Pfitzinger, J. prakt chem., 33, 100 (1886); (b) Cf. Buchman, J. Am. Chem. Soc., 68, 000 (1946).

[146] Sumpter, Chem. Rev., 34, 393 (1944).

[147] Van Ess, P.R., Doctoral Dissertation, Iowa State College (1936).

[148] Scholl and Seer, Ber., 44, 1241 (1911).

tives by a Friedel-Crafts reaction, but did not determine the positions of the substituents.

III. EXPERIMENTAL

The starting materials used in these investigations were commercial products of the highest purity unless otherwise indicated, and were used without further purification. The alkyl groups are the normal straight-chained groups. All of the melting and boiling points are uncorrected.

Dibutyldodecylamine. The dodecyl, tetradecyl and octadecyl bromides used in these investigations were prepared by the reactions of the alcohols with hydrobromic and sulfuric acids.[149]

A mixture of 49.8 g. (0.2 mole) of dodecyl bromide and 51.6 g. (0.4 mole) of dibutylamine was heated at a temperature of 140-155° for ten hours and, on cooling, the mixture formed two layers.

The reaction mass was refluxed with two 150 ml. portions of 10 percent sodium hydroxide for one hour. Subsequent to saturation of the aqueous layer with sodium chloride, the solution was extracted with ether. The ethereal solution was dried over anhydrous potassium carbonate.

Distillation of the ether and further distillation of the residue on a water bath at 20-30 mm. gave 24.7 g. (95%) of recovered dibutylamine. Fractionation of the residue gave 40.6 g. (68%) of a slightly yellow liquid; b.p. 158-160° (3.0 mm.);

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149. Kamm and Marvel, Organic Syntheses, Coll. Vol. I, 29, (1944).

n_D^{20} 1.4471; d_{20}^{20} 0.8073; MR calcd., 98.52; found, 98.32.

Anal. Calcd. for $C_{20}H_{43}N$: N, 4.71. Found: N, 4.76.

Dibutyltetradecylamine. This preparation followed the procedure described for the dodecyl homologue (p. 48). From 55.4 g. (0.2 mole) of tetradecyl bromide and 51.6 g. (0.4 mole) of dibutylamine heated at 140-150° for ten hours, there was recovered 23.8 g. (92%) of dibutylamine. Fractionation of the residue yielded 49.5 g. (76%) of a colorless liquid; b.p. 178-180° (3.0 mm.); n_D^{20} 1.4480; d_{20}^{20} 0.8046; MR calcd., 107.8; found, 108.1.

Anal. Calcd. for $C_{22}H_{47}N$: N, 4.31. Found: N, 4.62.

Dibutylhexadecylamine. This preparation followed the procedure described for the dodecyl homologue (p. 48). From 61 g. (0.2 mole) of hexadecyl bromide[150] and 51.6 g. (0.4 mole) of dibutylamine heated at 140-155° for ten hours, there was recovered 18.7 g. (72%) of dibutylamine. Distillation of the residue yielded 56.8 g. (81%) of a colorless opaque liquid; b.p. 203-205° (4.0 mm.); n_D^{20} 1.4500; d_{20}^{20} 0.8150; MR calcd., 117.0; found, 116.4.

Anal. Calcd. for $C_{24}H_{51}N$: N, 3.97. Found: N, 4.01.

Dibutyloctadecylamine. This preparation followed the procedure described for the dodecyl homologue (p. 48). From 50 g. (0.15 mole) of octadecyl bromide and 38.7 g. (0.3 mole) of dibutylamine heated at 140-155° for ten hours, there was

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150. This material was obtained from Edwal Laboratories, Chicago, Illinois, and the fraction distilling at 147-150° (3.0 mm.) was used in this preparation.

recovered 18 g. (93%) of dibutylamine. Fractionation of the residue gave 45 g. (79%) of a colorless liquid; b.p. 204-207° (3.0 mm.); n_D^{20} 1.4513; d_{20}^{20} 0.8192; MR calcd., 126.2; found, 125.3. This product became turbid on standing.

Anal. Calcd. for $C_{26}H_{55}N$: N, 3.68. Found: N, 3.88.

Dibutylaminomethyl butyl ether.[151] To a well stirred mixture of 222 g. (3.0 moles) of butanol-1 and 210 g. (1.63 moles) of dibutylamine was slowly added 45 g. (1.5 moles) of paraformaldehyde. After thirty minutes the solution cleared up and then became cloudy, indicating the presence of water. The mixture was stirred for an additional hour, and then 75 g. of anhydrous potassium carbonate was added after which the mixture was stirred for twenty-four hours.

The liquid was decanted from the potassium carbonate, and the solid was washed with 150 ml. of anhydrous ether. The ether washings were added to the decanted liquid, and the mixture distilled. After removal of the ether, distillation of the residue yielded 281 g. (83%) of a colorless liquid; b.p. 85-86° (0.15 mm.); n_D^{20} 1.4310. Stewart and Bradley give the boiling point as 116° (11 mm.) but give no yield and no other physical constants.

Dibutyltridecylamine. This preparation followed the method of Robinson and Robinson.[122] Dodecylmagnesium bromide was prepared in 77% yield from 50 g. (0.2 mole) of dodecyl bromide

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151. Stewart and Bradley, J. Am. Chem. Soc., 54, 4177 (1932).

and 5 g. (0.21 g. atom) of magnesium turnings in 200 ml. of anhydrous ether. The reaction was slow in starting.

To the well-stirred filtered Grignard solution (0.153 mole) was slowly added 32.2 g. (0.14 mole) of dibutylaminomethyl butyl ether. Reaction was quite vigorous, and when addition was complete, the mixture was refluxed for thirty minutes and allowed to stand for twenty-four hours. The mixture was filtered, and the ether removed by distillation. The residue would not distil at a bath temperature of 275° at 1.2 mm.

The mixture was taken up in 100 ml. of ether, and 30 ml. of 6N hydrochloric acid was added with thorough shaking. Fifty milliliters of water was added, and the two layers were separated. The aqueous layer was then extracted with two 100 ml. portions of ether, and the ethereal extracts were combined and dried over potassium hydroxide.

Removal of the ether and distillation of the residue yielded 22.7 g. (52%) of a colorless liquid; b.p. 144-148° (0.35 mm.); n_D^{20} 1.4485. A portion was redistilled for analysis; b.p. 120-122° (0.1 mm.); n_D^{20} 1.448; d_{20}^{20} 0.809; MR calcd., 103.2; found, 102.9.

Anal. Calcd. for $C_{21}H_{45}N$: N, 4.50. Found: N, 5.12.

Dibutyltridecylmethylammoniumiodide. This methiodide was prepared by refluxing a solution of the amine in methyl iodide for four hours. After removal of the excess methyl iodide, addition of anhydrous ether gave an oil which on standing in the icebox for forty-eight hours formed white plates. This product was filtered and washed twice with anhydrous ether to give white plates, melting at 52.0-52.5°.

Anal. Calcd. for $C_{22}H_{48}NI$: I, 28.04. Found: I, 28.03.

Octadecyl Chloride.[152] This compound was obtained in 87 percent yield from octadecyl alcohol and thionyl chloride. It was found necessary to purify the thionyl chloride by distillation from quinoline and then linseed oil[153] since the use of Eastman practical grade thionyl chloride gave an unresolvable mixture of alcohol and chloride.

Trioctadecylamine.[60] A mixture of 26 g. (0.05 mole) of dioctadecyl amine and 8 g. (0.028 mole) of octadecyl chloride was heated at 175-180° for eight hours. The mixture was then poured into a casserole and allowed to cool overnight.

The mixture was finely powdered under anhydrous ether three times, being filtered after each powdering. The residue was then extracted for twelve hours in a Soxhlet extractor with ether. Subsequent to drying there was obtained 12 g. of dioctadecylamine hydrochloride, m.p. 174-176°.

The ethereal extracts were combined and after distillation of the ether, the residue was heated with 250 ml. of one percent potassium hydroxide in fifty percent ethanol for one hour. Recrystallization from ethyl acetate gave 17.1 g. of

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[152] McCorkle, M.R., Doctoral Dissertation, Iowa State College (1938).

[153] Fieser, "Experiments in Organic Chemistry", Heath and Company, New York, (1941), Part II, p. 381.

material melting at 45-55°.

This product was suspended in 200 ml. of hot absolute ethanol and anhydrous hydrogen chloride gas passed into the mixture, all of the material going into solution. After the addition of three grams of Norite, the mixture was heated to reflux, and filtered. Cooling and filtration gave 14.6 g. of crude trioctadecylamine hydrochloride, m.p. 92-93°. Another ethanol-Norite treatment gave 12.8 g. (58%) of trioctadecylamine hydrochloride, m.p. 94-95°.

This hydrochloride was refluxed with two 100 ml. portions of 5 percent potassium hydroxide in 50 percent aqueous ethanol. The residue was recrystallized twice from ethyl acetate to give 10.1 g. (52%) of trioctadecylamine, m.p. 53-54°.

<u>α-Chloronaphthalene and Lithium Diethylamide.</u>[127] In a nitrogen atmosphere, lithium diethylamide was prepared in ether by the reaction of 18.3 g. (0.25 mole) of diethylamine in 100 ml. of ether with 0.2 mole of methyllithium in 100 ml. of ether. Then 32.6 g. (0.2 mole) of α-chloronaphthalene in 75 ml. of ether was added, and the mixture was stirred and refluxed for twenty-four hours. The color changes in the mixture during reaction were from brown to green to brownish-yellow, and a small amount of solid formed. Subsequent to hydrolysis by dilute hydrochloric acid, the ether layer was extracted with dilute hydrochloric acid. From the ether layer after drying over anhydrous sodium sulfate there was obtained by distillation 2.2 g. (8.5%) of pure naphthalene (mixed m.p.)

and 9 g. (27.5%) of recovered *α*-chloronaphthalene which was identified by a mixed melting point determination of its picrate with an authentic specimen of the picrate. From the hydrochloric acid solutions, subsequent to being made alkaline by sodium hydroxide solution, there was obtained a crude yield of 13.3 g. (33%) of *β*-diethylaminonaphthalene[154] which on redistillation yielded 10.0 g. (27%) of pure product. Identification was completed by formation of the *sym*-trinitrobenzene complex which melted at 114-115° and showed no depression in mixed melting point with an authentic specimen.[155]

α-Bromonaphthalene and Lithium Diethylamide.[127] By a procedure similar to the previous preparation, from 41.4 g. (0.2 mole) of *α*-bromonaphthalene and 0.2 mole of lithium diethylamide, there was isolated and identified, 2.2 g. (8.5%) of naphthalene, 10 g. (24%) of *α*-bromonaphthalene and 10.5 g. (27%) of *β*-diethylaminonaphthalene.

In a similar reaction in which the mixture was refluxed for six hours and then carbonated there was obtained a very small amount of a solid soluble in base, but this product could not be identified.

α-Fluoronaphthalene and Lithium Diethylamide.[127] Under conditions corresponding to that described for *α*-chloronaphthal-

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[154] This compound was also prepared in 71% yield by the method of Morgan, *J. Chem. Soc.*, *77*, 823 (1900) from the reaction of *β*-naphthylamine, ethyl iodide and sodium hydroxide in a sealed tube at 130-140° for seven hours.

[155] Hibbert and Sudborough, *J. Chem. Soc.*, *83*, 1340 (1903).

ene, there was obtained from 25.8 g. (0.18 mole) of α-fluoronaphthalene and 0.2 mole of lithium diethylamide, 14.3 g. (40%) of β-diethylaminonaphthalene and 6.2 g. of a mixture of what appeared to be naphthalene and α-fluoronaphthalene (which have essentially the same boiling points).

α-Bromonaphthalene and Lithium Didodecylamide. The didodecyl amine used in this experiment melted at 54-55° and was obtained from Armour & Co., Chicago, Ill. A nitrogen atmosphere was maintained.

To 8.1 g. (0.023 mole) of didodecylamine dissolved in 100 ml. of anhydrous ether was added with stirring 0.023 mole of methyllithium in 25 ml. of ether. Reaction was vigorous, and the solution turned milky white. After two and one-half hours of refluxing, color test I[156] was negative and color test IV[157] was positive.

A solution of 4.2 g. (0.02 mole) of α-bromonaphthalene in 20 ml. of anhydrous ether was added and the mixture refluxed. After twelve hours the mixture was green. After twenty-four hours the mixture was brownish-yellow, and color test IV was negative.

The mixture was poured into 100 ml. of water, and the layers separated. The aqueous layer was extracted with 50 ml.

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[156] Gilman and Schulze, *J. Am. Chem. Soc.*, *47*, 2002 (1925).

[157] Gilman and Woods, *ibid*, *65*, 33 (1943).

of ether, and the ethereal extracts were combined and dried over potassium carbonate.

After distillation of the ether, fractionation of the residue gave 1 g. (24%) of α-bromonaphthalene, identified by mixed m.p. of picrate, 2.9 g. (35%) of didodecylamine, identified by mixed m.p. (54-55°), and 5 g. of brown liquid; b.p. 230-250° (0.05-0.10 mm.); n_D^{20} 1.5145.

This brown liquid was redistilled to give 4.5 g. (42%) of brown liquid; b.p. 215-220° (0.05 mm.); 220-240° (0.10 mm.); n_D^{20} 1.5155. The boiling point appeared to be quite dependent on the bath temperature.

The product did not form a picrate nor a 1,3,5-trinitrobenzene addition product. Attempts at coupling the product with p-nitrobenzenediazonium chloride in acetone[158] were unsuccessful.

Five-tenths grams (0.001 mole) of the product was dissolved in 5 ml. of ether, and 0.004 mole of ethereal hydrogen chloride was added. The ether was then removed, and the residue taken up in 3 ml. of ethyl acetate. After two recrystallizations from ethyl acetate, the product softened at 87°, melted at 90-91°. A mixed melting point sample with an authentic specimen of β-didodecylaminonaphthalene hydrochloride (m.p. 94-95°), melted at 93-94°.

βN-Dodecylaminonaphthalene. A mixture of 43 g. (0.3 mole) of β-naphthylamine and 25 g. (0.1 mole) of dodecyl bro-

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[158] Hickinbottom and Lambert, J. Chem. Soc., 1384 (1939).

mide in 60 ml. of absolute ethanol was gently refluxed on an oil bath for 24 hours, all of the material going into solution. The excess ethanol was removed under reduced pressure, and the solid extracted repeatedly with 600 ml. of ether. The mixture was filtered, the ether removed and the precipitate extracted with the condensed ether. There was left 20 g. of solid material (probably β-naphthylamine hydrochloride).

Removal of the ether and distillation of the residue gave the following fractions: (1) 14 g., b.p. 115-122° (0.6 mm.); solidifying to a white product, m.p. 107-109°; mixed m.p. with authentic β-naphthylamine, 109-110°; (2) 28.1 g., b.p. 184-225° (0.07-0.4 mm.), solidifying to a brownish product, m.p. 39-42°.

Recrystallization of fraction 2 from 65 ml. of 95 percent ethanol gave 26.1 g. (83%) of a white solid, melting at 41-43°. β-N-Dodecylaminonaphthalene has been reported to melt at 41-43°.[159]

β-N,N-Didodecylaminonaphthalene. A mixture of 26 g. (0.0836 mole) of β-N-dodecylaminonaphthalene, 21 g. (0.0836 mole) of dodecyl bromide and 10 g. of anhydrous sodium carbonate in 120 ml. of 95 percent ethanol was refluxed for forty-five hours. A portion of the ethanol was removed under reduced pressure and a solution of 10 g. of anhydrous sodium carbonate in 100 ml. of water was added. The mixture was refluxed twenty minutes and cooled.

The mixture was extracted with 200 ml. of ether in three

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[159] Butterworth and Hey, ibid, 388 (1940).

portions. The ethereal extracts were combined and washed with water until neutral. Twenty-five milliliters of ether was added, and the ethereal extracts were dried over anhydrous potassium carbonate.

After removal of the ether, distillation of the residue gave the following fractions: (1) 9 g., b.p. 94-96° (0.7 mm.); (2) 12.0 g., b.p. 203-230° (0.7 mm.); (3) 18.0 g., b.p. 260-276° (0.8 mm.); partially solidifying on cooling.

Redistillation of Fraction 3 gave the following fractions: (a) 2.4 g., b.p. 196-235° (0.3 mm.) and (b) 15.1 g. (37%), b.p. 255-260° (0.5 mm.); n_D^{20} 1.5310; d_{20}^{20} 0.911.

Anal. Calcd. for $C_{34}H_{57}N$: N, 2.92. Found: N, 3.17.

The hydrochloride was prepared in ether from 3 g. (0.006 mole) of fraction (b) and 0.011 mole of ethereal hydrogen chloride. After recrystallization from ethyl acetate, 2.1 g. of white product was obtained, melting at 94-95°.

Anal. Calcd. for $C_{34}H_{58}NCl$: Cl, 6.88. Found: Cl, 7.01 and 7.06.

p-Chlorophenyl Dodecyl Ether and Lithium Diethylamide. The *p*-chlorophenyl dodecyl ether was kindly furnished by L. F. Cason and had the following constants: b.p. 165-166° (0.5 mm.); n_D^{20} 1.4960.

Lithium diethylamide was prepared in a nitrogen atmosphere from 6 g. (0.08 mole) of diethylamine and 0.074 mole of methyllithium in 100 ml. of ether. When reaction was complete (negative color test I), 21 g. (0.072 mole) of *p*-chlorophenyl dodecyl ether in 25 ml. of ether was added. The milky-white mixture turned slightly yellow. The mixture was refluxed for 24 hours and became more yellow. On cooling, a solid settled out.

This product was poured into 100 ml. of water, shaken well, 50 ml. of concentrated hydrochloric acid added and the resulting mixture shaken again. Very little color passed into the acid layer. The ether layer was extracted again with 90 ml. of 4N hydrochloric acid. The ethereal layer was washed with water and 10% sodium hydroxide solution and dried over anhydrous potassium carbonate (Solution I).

The combined acid extracts were made basic with 20 percent sodium hydroxide solution but very little oil appeared. The solution was extracted with ether, and the ethereal layer dried over anhydrous sodium sulfate (Solution II). Removal of the ether gave a few drops of an oil, but this product would not form a picrate.

Passage of anhydrous hydrogen chloride gas into a sample of the dried ethereal solution (I) did not give a precipitate.

Distillation of the residue after removal of the ether from Solution I gave the following fractions: (1) 8.9 g., b.p. 155-175° (0.7 mm.); n_D^{20} 1.4939; (2) 5.3 g., b.p. 175-190° (0.7 mm.); n_D^{20} 1.5005; (3) 2.5 g., b.p. 180-188° (0.5 mm.); n_D^{20} 1.5049. The residue (1.5 g.) was dissolved in ethanol but did not form a picrate.

The above fractions were combined and redistilled to give the following fractions: (a) 7.8 g., b.p. 155-164° (0.7 mm.) and 175-190° (0.7 mm.); n^{20}_{D} 1.5009; (b) 7.0 g., b.p. 164-174° (0.7 mm.); n^{20}_{D} 1.4951. This amount (14.8 g.) is a 68 percent recovery.

Purification of Tetradecylamine. Two hundred grams of crude tetradecylamine[160] was dissolved in 250 ml. of absolute ethanol with heating. The mixture was then cooled and after the addition of 150 ml. of concentrated hydrochloric acid it was chilled to 0°.

The precipitate was filtered and washed with anhydrous ether to give 185 g. (89%) of tetradecylamine hydrochloride.

To a suspension of fifty grams of the hydrochloride in 500 ml. of ether was added 100 g. of ice and a cool solution of 50 g. of sodium hydroxide in 200 ml. of water. The mixture was shaken until the ice melted. The aqueous layer was extracted with 100 ml. of ether, the ethereal solutions combined, washed with water and dried over sodium hydroxide.

The ether was removed by distillation, and the residue distilled to give 36 g. (85%) of a colorless liquid; b.p. 100-101° (0.15 mm.), solidifying to a solid melting at 36-37°. The melting point of tetradecylamine has been reported to be 37°.[161]

Purification of Hexadecylamine. Two hundred grams of

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[160] These amines were obtained from Armour & Co., Chicago, Illinois.

[161] Krafft, Ber., 23, 2361 (1890).

99% hexadecylamine[160] was dissolved in 500 ml. of warm absolute ethanol. To the cooled solution was added 150 ml. of concentrated hydrochloric acid and the resulting mixture was chilled to 0°. Filtration and air-drying gave a quantitative yield (232 g.) of hexadecylamine hydrochloride.

Fifty grams of the hydrochloride was decomposed as described under tetradecylamine. There was obtained 29.5 g. (69%) of hexadecylamine; b.p. 120-130° (0.25 mm.); m.p. 47-48°. The reported melting point of this compound is 45-46°.[162]

Harber has emphasized the basicity of these amines and the subsequent precautions necessary in the preparation of their derivatives. Consequently, these amines were kept in tightly stoppered bottles and had the minimum exposure to moisture and carbon dioxide.

N,N'-Ditetradecyloxalamide. To a warmed solution of 4 g. (0.027 mole) of ethyl oxalate in 35 ml. of 95 percent ethanol was added with vigorous stirring a solution of 10.7 g. (0.05 mole) of tetradecylamine in 35 ml. of 95 percent ethanol. Precipitation occurred very quickly. Thirty-five milliliters of 95 percent ethanol was added, and the mixture stirred for fifteen minutes longer. The product was cooled and filtered.

The crude product was recrystallized from petroleum ether (b.p., 77-115°) to give 9.3 g. (79%) of white plates, melting at 118-119°. Further recrystallization did not change the melting point.

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[162] Krafft and Maye, Ber., 22, 812 (1889).

Anal. Calcd. for $C_{30}H_{60}O_2N_2$: N, 5.83. Found: N, 5.55.

N,N'-Dihexadecyloxalamide. To a warmed solution of 4 g. (0.027 mole) of ethyl oxalate in 35 ml. of 95 percent ethanol was added with vigorous stirring a solution of 12.1 g. (0.05 mole) of hexadecylamine in 35 ml. of 95 percent ethanol. Precipitation was immediate. Thirty-five milliliters of 95 percent ethanol was added, and the mixture stirred for fifteen minutes longer. The mixture was cooled and filtered.

The crude product was recrystallized from petroleum ether (b.p., 77-115°) to give 11.7 g. (87%) of a white solid, melting at 119-120°. Further recrystallization did not change the melting point.

Anal. Calcd. for $C_{34}H_{68}O_2N_2$: N, 5.22. Found: N, 5.61.

N,N'-Ditetradecylthiourea. To a solution of 10.7 g. (0.05 mole) of tetradecylamine in 50 ml. of absolute ethanol was added a solution of 4.2 g. (0.055 mole) of freshly distilled carbon disulfide in absolute ethanol. A vigorous reaction occurred immediately, and the mixture set solid. The mixture was refluxed for 48 hours and solidified on cooling. The ethanol was removed under reduced pressure on the steam bath. After cooling there remained 10.7 g. (92%) of a light cream solid, softening at 77°, melting at 78-79°. Recrystallization from absolute ethanol gave 9.3 g. (81%) of a white solid, melting at 80-81°. Further recrystallization did not change the melting point.

Anal. Calcd. for $C_{29}H_{60}N_2S$: N, 6.00. Found: N, 6.05.

N,N'-Dihexadecylthiourea. To a solution of 12.1 g. (0.05 mole) of hexadecylamine in 50 ml. of absolute ethanol was added a solution of 4.2 g. (0.055 mole) of freshly distilled carbon disulfide in absolute ethanol. A vigorous reaction took place at once, and the mixture set solid. The mixture was refluxed for 48 hours and solidified on cooling. The ethanol was removed under reduced pressure on the steam bath. The crude residue was recrystallized from absolute ethanol to give 13 g. (quantitative) of material melting at 85-86°. Recrystallization from absolute ethanol gave a white solid melting at 87-88°.

Anal. Calcd. for $C_{33}H_{68}N_2S$: N, 5.34. Found: N, 5.29. This product has been reported to melt at 88-89°.[133]

N-Tetradecyl-N'-phenylthiourea. To 5.4 g. (0.025 mole) of molten tetradecylamine in a 125 ml. Erlenmeyer flask was added 3.7 g. (0.0255 mole) of phenyl isothiocyanate. Reaction was immediate and exothermic, and the yellowish liquid which formed solidified on cooling. The product was allowed to stand for 24 hours. There was obtained 7.5 g. (86%) of white plates melting at 70-72°. The material was recrystallized to constant melting point, 77.5-78°, from absolute ethanol.

Anal. Calcd. for $C_{21}H_{36}N_2S$: S, 9.22. Found: S, 8.96.

N-Hexadecyl-N'-phenylthiourea. To 6.1 g. (0.025 mole) of molten hexadecylamine in a 125 ml. Erlenmeyer flask was added 3.7 g. (0.0255 mole) of phenyl isothiocyanate. The reaction was immediate and exothermic, and the yellowish liquid which formed solidified on cooling. The product was allowed to stand for 24 hours. There was obtained 8.9 g. (94%) of a white solid melting at 78-79°. The material was recrystallized to a constant melting point of 82-82.5° from absolute ethanol.

Anal. Calcd. for $C_{23}H_{40}N_2S$: S, 8.50. Found: S, 8.51.

N-Tetradecylurea. A finely ground mixture of 26.0 g. (0.105 mole) of tetradecylamine hydrochloride and 16.2 g. (0.2 mole) of potassium cyanate in 500 ml. of 95 percent ethanol was evaporated to dryness in a large evaporating dish. The residue was powdered and heated for thirty minutes with 800 ml. of absolute ethanol and filtered hot from the potassium chloride. The filtrate was cooled in the ice-box.

Filtration and drying gave 22.5 g. (88%) of material melting at 112-113°. Recrystallization from ethanol did not change the melting point. This product has been prepared[117] from nitrourea and tetradecylamine and melted at 114.5°.

N-Hexadecylurea. A finely ground mixture of 28.8 g. (0.1 mole) of hexadecylamine hydrochloride and 16.2 g. (0.2 mole) of potassium cyanate in 500 ml. of 95 percent ethanol was evaporated to dryness in a large evaporating dish. The residue was powdered and heated for thirty minutes with 800 ml. of absolute ethanol. The product was filtered hot from the potassium chloride, and the filtrate was cooled in the ice-box.

Filtration and drying gave 26.3 g. (92%) of product, melting at 106-107°. Recrystallization from ethanol did not change the melting point. This product has been prepared[117] from nitrourea and hexadecylamine and melted at 108.5°.

N- -Tetradecylbenzenesulfonamide. To 4.3 g. (0.02 mole) of tetradecylamine in a 125 ml. Erlenmeyer flask was added 40 ml. of warm (40°) 15 percent potassium hydroxide solution and 5.3 g. (0.03 mole) of benzenesulfonyl chloride in two portions. The flask was stoppered and shaken vigorously after each addition of the acid chloride. The reaction mixture became warm and at the end of the shaking there was no odor of unchanged benzenesulfonyl chloride. The partially solidified mixture was poured into 40 ml. of water and warmed. An excess of hydrochloric acid was added, and the mass cooled below room temperature. The material solidified and was filtered, washed with water and dried to give 6.9 g. of white product, melting at 60-62°. The product was recrystallized from absolute ethanol to give 5.5 g. (79%) of white crystals, melting at 65-66°.

An analytical sample crystallized from methanol as white needles, melting at 66-67°.

Anal. Calcd. for $C_{20}H_{35}O_2NS$: S, 9.06. Found: S, 8.86.

N-Hexadecylbenzenesulfonamide. To 4.8 g. (0.02 mole) of hexadecylamine in a 125 ml. Erlenmeyer flask was added 50 ml. of warm (50°) 15 percent potassium hydroxide, and the mixture was warmed to 60°. To this warm solution was added 5.3 g. (0.03 mole) of benzenesulfonyl chloride in three portions. The reaction mixture became very warm and at the end of the shaking there was no odor of unchanged benzenesulfonyl chloride. The partially solidified mixture was poured into 50 ml. of water, a solid precipitating. The solution was made acid with hydrochloric acid, stirred well, filtered and washed with water.

The wet precipitate was recrystallized from methanol to give 7.0 g. (92%) of white fatty crystals, melting at 70-71°. Recrystallization from methanol did not change the melting point.

Anal. Calcd. for $C_{22}H_{39}O_2NS$: S, 8.40. Found: S, 8.26.

5-Nitro-6-quinolyl Methyl Sulfide. To 2 g. (0.0096 mole) of 5-nitro-6-chloroquinoline dissolved in 25 ml. of methyl cellosolve at room temperature was added dropwise 0.012 mole of sodium methyl mercaptide in 15 ml. of methyl cellosolve in a nitrogen atmosphere. The mixture became yellow, and as reaction proceeded, a solid precipitated. The mixture was stirred for an hour at room temperature and then poured into 250 ml. of water. The yellow precipitate was allowed to stand for an hour, filtered and dried to give 2.0 g. (94%) of yellow crystals, melting at 138-139°. Recrystallization from 600 ml. of petroleum ether (b.p., 60-68°) gave 1.85 g. of yellow crystals, melting at 138.5-139°.

When this reaction was run at the reflux temperature of methyl cellosolve, the mixture became very dark and only 0.3 g. of product, melting at 136-138° was obtained from 2 g. of 5-nitro-6-chloroquinoline.

Anal. Calcd. for $C_{10}H_8O_2N_2S$: S, 14.55. Found: S, 14.53.

5-Nitro-6-quinolyl Dodecyl Sulfide. To a solution of 10 g. (0.048 mole) of 5-nitro-6-chloroquinoline in 100 ml. of methyl cellosolve was slowly added a cooled solution of sodium dodecyl mercaptide, prepared from 1.1 g. (0.048 g. atom) of sodium and 9.8 g. (0.048 mole) of dodecyl mercaptan[163] in 60 ml. of methyl cellosolve. This reaction was run in an atmosphere of nitrogen.

As addition proceeded the mixture warmed up and became cloudy with formation of salt. The mixture was stirred at room temperature for two and three-quarter hours and then heated at 60-65° for two hours. The product was poured into 600 ml. of water with stirring. Filtration was difficult so the mixture was made slightly acid with acetic acid, after which filtration was easier. Drying gave 17.2 g. (95%) of yellow material, softening at 41°, melting at 42-43°. Recrystallization from 200 ml. of methanol gave 14.7 g. (80%) of yellow crystals, melting at 44-45°. Further recrystallization did not raise the melting point.

Anal. Calcd. for $C_{21}H_{30}O_2N_2S$: S, 8.56. Found: S, 8.50.

When this reaction was run at the reflux temperature of ethanol, a mixture was obtained which could not be purified.

5-Amino-6-quinolyl Dodecyl Sulfide. Fourteen and seven-

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[163] The dodecyl, tetradecyl and hexadecyl mercaptans used in these investigations were obtained from Connecticut Hard Rubber Co., New Haven, Conn. The dodecyl and tetradecyl mercaptans were purified by L. F. Cason.

tenths grams (0.038 mole) of 5-nitro-6-quinolyl dodecyl sulfide was dissolved in 200 ml. of absolute ethanol, one teaspoon of Raney nickel[164] was added and the mixture shaken under 60 pounds pressure of hydrogen. Reduction was very slow requiring six hours.

The nickel was filtered off, the ethanol removed under reduced pressure and the residue washed with 25 ml. of petroleum ether, (b.p., 60-68°) to give 10.2 g. (76%) of yellow product, melting at 59-60°. Recrystallization from petroleum ether (b.p., 60-68°) did not change the melting point.

Anal. Calcd. for $C_{21}H_{32}N_2S$: S, 9.30. Found: S, 9.02.

5-Acetamido-6-quinolyl Dodecyl Sulfide.[165] One gram (0.002 mole) of 5-nitro-6-quinolyl dodecyl sulfide was dissolved in 5 ml. of glacial acetic acid, and the solution heated just to reflux. One and five-tenths ml. (0.015 mole) of acetic anhydride was added, and the mixture refluxed for fifteen minutes, poured into water and allowed to stand for three hours. Filtration and drying gave 0.9 g. (83%) of white material melting at 110-115°. The product was recrystallized from absolute ethanol to a constant melting point of 121-122°.

Anal. Calcd. for $C_{23}H_{34}ON_2S$: S, 8.29. Found: S, 8.21.

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164. Mozingo, Organic Syntheses, 21, 15 (1941).

165. The name acetamido is used in accordance with the nomenclature recommended by Chemicals Abstracts, (1945). The name, acetamino, however, is more commonly used.

5-α-Hydroxybenzylideneamino-6-quinolyl Dodecyl Sulfide (attempted). A mixture of 0.33 g. (0.0027 mole) of salicylaldehyde and one gram (0.0027 mole) of 5-amino-6-quinolyl dodecyl sulfide in 6 ml. of absolute ethanol was refluxed for one hour and then allowed to cool in ice for four hours. No crystallization occurred. The ethanol was removed under reduced pressure and the thick oil chilled, but no crystallization occurred. Three milliliters of methanol was added, and the mixture placed in the ice-box for twelve hours, wherein crystallization occurred. Filtration gave 0.3 g. of product, m.p. 59-60°, mixed m.p. with starting amine, 59-60°. Three-tenths grams more of product was obtained, melting at 59-60°. No evidence of reaction was obtained.

5-(2',5'-Dimethylpyrryl)-6-quinolyl Dodecyl Sulfide (attempted. *Method A*. This preparation followed the method of Hazelwood, Hughes, and Lions.[166] A mixture of 0.31 g. (0.0027 mole) of acetonylacetone, one gram (0.0027 mole) of 5-amino-6-quinolyl dodecyl sulfide, five ml. of absolute ethanol and eleven drops of glacial acetic acid was refluxed for four hours. The mixture was then chilled for two hours, but no crystallization occurred. The mixture was poured into 250 ml. of cold water with stirring, and the product slowly crystallized. After standing in the ice-box for twenty-four hours, filtration and drying gave 0.9 g. of recovered starting amine (mixed m.p.,

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166. Hazelwood, Hughes, Lions, and co-workers, *J. Proc. Roy. Soc. N.S. Wales*, *71*, 92 (1937) [*C.A.*, *32*, 1695 (1938)].

59-60°).

Another run using 2.31 g. (0.02 mole) of acetonylacetone, one gram (0.0027 mole) of amine, five ml. of absolute ethanol and eleven drops of glacial acetic acid also gave 0.8 g. of recovered starting amine (mixed m.p.).

Method B. Two grams (0.0054 mole) of 5-amino-6-quinolyl dodecyl sulfide and 2 g. (0.017 mole) of acetonylacetone were mixed together and heated to 100°, all of the material going into solution. Approximately one-half drop of concentrated hydrochloric acid was added and a small amount of a yellow precipitate formed. The mixture was heated at 110-120° for two hours and then the temperature was raised to 150-160° for one hour, and then to 160-180° for an additional hour. The mixture was cooled and poured into water, an oil forming which slowly solidified. The product was allowed to stand for twelve hours. Attempts to recrystallize the solid (after decantation of the water) from methanol or petroleum ether (b.p., 60-68°) were unsuccessful. The product darkened on standing and was then taken up in 350 ml. of ether and dried over anhydrous sodium sulfate.

Removal of the ether left an oil which would not solidify on chilling. Attempts to prepare a picrate were unsuccessful.

5-(ϵ-Isopropylaminopentylamino)-6-quinolyl Dodecyl Sulfide Hydrochloride (attempted). *Method A*.[167] A mixture of

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[167] Cf. Rohrmann and Shonle, *J. Am. Chem. Soc.*, *66*, 1642 (1944).

3.4 g. (0.01 mole) of 5-amino-6-quinolyl dodecyl sulfide, 2 g. (0.01 mole) of *ε*-isopropylaminopentyl chloride hydrochloride was dissolved in 20 ml. of warm absolute ethanol. Three grams (0.01 mole) of sodium citrate was added, and the mixture stirred with refluxing. The mixture began to thicken, and after 12 hours an additional ten milliliters of ethanol was added. The mixture was refluxed with stirring for forty-eight hours. The mixture was cooled and poured into cold water with formation of a solid. The mixture was made basic with ammonium hydroxide and filtered. Drying gave 3.4 g. of recovered starting amine, m.p. 55-57°, mixed m.p. 59-60°.

Method B. A mixture of the above recovered amine, 3.4 g. (0.01 mole), 2.3 g. (0.011 mole) of *ε*-isopropylaminopentyl chloride hydrochloride and 5 ml. of absolute ethanol was heated on a boiling water bath for one hour. The reflux condenser was replaced by a short tube, and the mixture was heated at a bath temperature of 110-120° for ten hours and then at 130-140° for six hours. The mixture was allowed to cool and taken up in 500 ml. of water. The solution was made basic with ammonium hydroxide, extracted with ether and dried over sodium sulfate.

The ether solution was filtered and concentrated to *ca.* 150 ml. A hydrochloride was prepared by the addition of 0.03 mole of ethereal hydrogen chloride in 50 ml. of anhydrous ether. Filtration gave a dark red mass which could not be recrystallized from ethanol, ethyl acetate, a mixture of chloroform and petroleum ether, (b.p., 60-68°), a mixture of ethanol and ethyl acetate or a mixture of ethanol and ether.

The product was then taken up in 100 ml. of absolute ethanol, refluxed with _ca._ one gram of Norite, filtered and concentrated to _ca._ 20 ml. Cooling gave 0.7 g. (17%) of orange product, melting at 155-157°. An analytical sample, recrystallized from ethanol-ethyl acetate, melted at 156-157°. This product proved to be 5-amino-6-quinolyl dodecyl sulfide dihydrochloride.

Anal. Calcd. for $C_{21}H_{32}N_2S\cdot 2HCl$: S, 7.69. Found: S, 7.67.

The product was further identified by conversion to the free amine with ammonium hydroxide (mixed m.p.).

8-Amino-5-nitro-6-quinolyl Methyl Sulfide.[168] To a refluxing solution of 32.5 g. (0.12 mole) of 5-nitro-6-chloro-8-acetamidoquinoline in 400 ml. of methyl cellosolve was added a solution of 0.14 mole of sodium methyl mercaptide in 150 ml. of methyl cellosolve. The addition required ten minutes, and a solid precipitated during the addition. The mixture was refluxed for fifty minutes and allowed to cool. Filtration and washing with water gave 24.8 g. (88%) of orange crystals melting at 243-244°. Recrystallization from methyl cellosolve did not change the melting point. The product is unusually insoluble in most organic solvents.

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[168] Gilman, Benkeser, Gainer, Lindblad, Marshall, Massie, Myers, and Tolman, _J. Am. Chem. Soc._, _68_, 000 (1946).

This reaction was also carried out with ten minutes reflux in 83 percent yield.

Anal. Calcd. for $C_{10}H_9O_2N_3S$: N, 17.87; S, 13.61. Found: N, 18.41 and 18.33; S, 13.49 and 13.31.

8-Amino-5-nitro-6-quinolyl Dodecyl Sulfide. To 2.3 g. (0.0086 mole) of 5-nitro-6-chloro-8-acetamidoquinoline dissolved in 50 ml. of hot methyl cellosolve was added dropwise a solution of sodium dodecyl mercaptide, prepared from 0.23 g. (0.01 g. atom) of sodium and 2 g. (0.01 mole) of dodecyl mercaptan in 25 ml. of methyl cellosolve. The mixture was refluxed for an hour and allowed to cool. The mixture was poured into 200 ml. of water with stirring, made acid with acetic acid and filtered to give 3.7 g. (quantitative) of orange material melting at 85-87°. Recrystallization from 75 ml. of methanol gave 3.1 g. (93%) of orange material melting at 88-89°.

A sample recrystallized from methanol and treated with Norite melted at 89.5-90.5 and recrystallization did not change the melting point.

Anal. Calcd. for $C_{21}H_{31}O_2N_3S$: S, 8.23. Found: S, 8.30.

8-Acetamido-5-nitro-6-quinolyl Dodecyl Sulfide. Fourteen grams (0.036 mole) of 8-amino-5-nitro-6-quinolyl dodecyl sulfide was dissolved in 140 ml. of glacial acetic acid and heated to reflux. To the warm solution 15 ml. (0.15 mole) of acetic anhydride was added, and the mixture was refluxed for thirty minutes. The mixture was allowed to cool, poured onto ice, partially neutralized with ammonium hydroxide and filtered. The precipitate was recrystallized from 600 ml. of 95 percent ethanol to give 14.6 g. (94%) of yellow crystals melting at 67-68°.

Anal. Calcd. for $C_{23}H_{33}O_3N_3S$: S, 7.42. Found: S, 7.29.

8-Acetamido-5-amino-6-quinolyl Dodecyl Sulfide. A solution of 7.5 g. (0.0174 mole) of 8-acetamido-5-nitro-6-quinolyl dodecyl sulfide in 200 ml. of absolute ethanol with the addition of one teaspoon of Raney nickel[164] was shaken under 60 pounds pressure of hydrogen at the temperature of steam for two hours. The cooled solution was filtered, 20 ml. of benzene added and the solvents removed under reduced pressure. To the dark residue was added 50 ml. of petroleum ether (b.p., 60-68°), and the mixture was heated to reflux. All of the material did not go into solution. On cooling the product formed an oil, which on standing for 12 hours crystallized as a yellow solid. Filtration gave 5.6 g. (80%), melting at 77-78°.

Attempts at purification of this product were unsuccessful, as from petroleum ether (b.p., 30-40°, 60-68° or 77-115°) the product oiled on cooling and slowly crystallized to a yellow solid. The product was too soluble in methanol or ethanol.

Anal. Calcd. for $C_{23}H_{35}ON_3S$: S, 7.98. Found: S, 6.86 and 7.07.

5,8-Diacetamido-6-quinolyl Dodecyl Sulfide. The above amine was acetylated using acetic anhydride and acetic acid. Recrystallization from methanol with the use of Norite gave a cream-colored solid, melting at 126-127°.

Anal. Calcd. for $C_{25}H_{37}O_2N_3S$: N, 9.48. Found: N, 9.48.

2-Hydroxy-6-methoxylepidine.[169] To a cooled solution (5°) of 150 ml. of concentrated sulfuric acid in an ice-bath was added with stirring 200 g. of p-acetoacetanisidide (0.967 mole) with stirring at such a rate that the temperature of the mixture did not rise above 35°. The ice-bath was replaced by a water bath at room temperature and the bath was heated gradually to 90°. The mixture was then heated at 95-100° for two hours.

The hot dark syrup was poured into two and one-half liters of ice water with vigorous stirring. The pasty product was filtered, washed with water and dried as thoroughly as possible on the funnel.

The pasty solid was transferred to a 4-liter beaker, covered with water and made basic with concentrated ammonium hydroxide. The solid was filtered, washed with water and dried for eight hours at 140° to give 158 g. (87%) of a grayish powder melting at 259-260°.

This preparation was adapted to runs of 1000 grams of p-acetoacetanisidide in 85% yield.

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169. This preparation was adapted from directions kindly supplied by Dr. K. N. Campbell, University of Notre Dame, South Bend, Ind.

2-Chloro-6-methoxylepidine.[169] A mixture of 300 ml. of redistilled phosphorus oxychloride (b.p. 105-107°) and 100 g. (0.53 mole) of 2-hydroxy-6-methoxylepidine was heated in an oil bath at 110-112° (bath temperature). The phosphorus oxychloride refluxed and the solid material dissolved. After five minutes of heating the mixture solidified with vigorous refluxing. The mixture was heated at a bath temperature of 110-120° for two hours.

The product was cooled to 40°, and the excess phosphorus oxychloride was removed under reduced pressure, care being taken that the inner temperature did not exceed 50°. After removal of the phosphorus oxychloride, the residue was removed from the flask and cautiously added to 500 ml. of ice water. The product was filtered and washed well with water until free of acid. Air drying gave 115 g. of product, melting at 143-145°. The product was recrystallized by dissolving as much of the material as possible in 500 ml. of 95 percent ethanol at the reflux temperature. The insoluble material was filtered from the hot ethanol solution. This solution was chilled, and after removal of the crystallized solid, the filtrate was used to dissolve more of the insoluble material. This process was repeated until all of the material was dissolved and 91.5 g. (84%) of the purified solid, melting at 144-145°, was obtained.

The product may also be purified by recrystallization from methyl cellosolve, or by distillation. Fifty grams of crude product was distilled at 172-174° (0.1 mm.) to give 36

g. (72%) of material melting at 145-146°.

<u>6-Methoxylepidine Hydrate.</u>[169] A mixture of 100 g. (0.483 mole) of recrystallized 2-chloro-6-methoxylepidine, 38 g. of potassium hydroxide, 1400 ml. of 95 percent ethanol and 8 teaspoons of Raney nickel was placed in a three and one-half liter steel bomb and shaken at a pressure of 250 pounds of hydrogen with an initial temperature of 60°. After one hour, the theoretical amount of hydrogen appeared to be absorbed, but the mixture was shaken for another hour.

The nickel was filtered and the excess ethanol removed under reduced pressure. The residue was poured into 100 ml. of ice water and stirred until crystalline. Subsequent filtration and drying gave 90 g. (98%) of slightly brown material, melting at 50-2°.

This procedure was also adapted to runs of 200 g. in 98% yield.

<u>6-Methoxy-4-methyl-2-quinolyl Dodecyl Sulfide.</u> To a solution of five grams (0.024 mole) of 6-methoxy-2-chlorolepidine in 50 ml. of warm methyl cellosolve, was added dropwise a solution of sodium dodecyl mercaptide, prepared from 0.056 g. (0.024 g. atom) of sodium and 5 g. (0.024 mole) of dodecyl mercaptan in 50 ml. of methyl cellosolve. The mixture was refluxed for five and one-half hours with the formation of much salt. The product was poured into 500 ml. of water, made acid with acetic acid, filtered and dried to give 8.3 g. (93%) of cream material, melting at 65-67°. This product was recrys-

tallized from 200 ml. of methanol to give 6.3 g. (70%) of cream-colored material melting at 71-72°. A sample recrystallized for analysis melted at 73-74°.

Anal. Calcd. for $C_{23}H_{35}ONS$: S, 8.58. Found: S, 8.70.

7-Chloro-4-quinolyl Dodecyl Sulfide. To five grams (0.025 mole) of 4,7-dichloroquinoline in 50 ml. of hot methyl cellosolve was slowly added with stirring a solution of sodium dodecyl mercaptide, prepared from 0.57 g. (0.025 g. atom) of sodium and 5 g. (0.025 mole) of dodecyl mercaptan in 50 ml. of methyl cellosolve. Toward the end of the addition, a solid precipitated. The mixture was refluxed for one hour with further precipitation. The mixture was cooled, poured into 600 ml. of water, made acid with acetic acid and filtered. Filtration was difficult. Drying gave 7.9 g. (87%) of white material, melting at 58-59°. Recrystallization from methanol raised the melting point to 59-60°, and further recrystallization did not change the melting point.

Anal. Calcd. for $C_{21}H_{30}NSCl$: S, 8.80. Found: S, 8.90.

1-Diethylamino-2,3-epoxypropane.[170] A mixture of 112 g. (12.0 moles) of epichlorohydrin, 864 g. (11.8 moles) of diethylamine and 36 g. of water was stirred for six hours at a temperature of 28-30°. The solution was cooled to 20°, and a

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[170] This preparation was adapted from a N.D.R.C. report submitted by the laboratory of Columbia University. This compound was also prepared by Drozdov and Cherntov, *J. Gen. Chem.* (*U.S.S.R.*), *4*, 969 (1934) [*C.A.*, *29*, 2148 (1935)]; Eisleb, U.S. Patent, 1,845,403 (1932) [*C.A.*, *26*, 2199 (1932)].

solution of 560 g. (14 moles) of sodium hydroxide in 912 ml. of water was added at such a rate that the reaction temperature did not exceed 25°. The mixture was stirred for forty minutes after the addition of the base and then poured into two liters of water. The organic layer was separated and the aqueous layer was extracted with two 200 ml. portions of ether. The oil and the ethereal extracts were combined and dried over potassium hydroxide.

The excess solvent was removed by distillation at atmospheric pressure, and the residue was distilled at 58-60° (20-25 mm.) to give 950 g. (62%) of a colorless oil. The material must be stored in the ice-box and becomes cloudy on standing.

3-Diethylamino-2-hydroxypropyl Dodecyl Sulfide. The apparatus used for this and the four subsequent preparations consisted of a 500 ml., three-necked, round-bottomed flask, fitted with a stirrer, a condenser and a dropping funnel and arranged for maintenance of a nitrogen atmosphere.

A solution of 20.2 g. (0.1 mole) of dodecyl mercaptan in 50 ml. of toluene was added dropwise over a period of thirty minutes to a suspension of 2.3 g. (0.1 g. atom) of finely-cut sodium in 100 ml. of refluxing toluene. The mixture was refluxed for thirty minutes with disappearance of the sodium.

A solution of 12.9 g. (0.1 mole) of 1-diethylamino-2,3-epoxypropane in 25 ml. of toluene was added to the refluxing solution. Reaction was immediate and vigorous, much foaming occurring with disappearance of the sodium mercaptide.

The mixture was refluxed for six hours, cooled and 200 ml. of water added with stirring. A thick emulsion formed. The emulsion was allowed to separate over a period of twelve hours. The toluene layer was separated, and the aqueous layer extracted in two portions with 250 ml. of ether. The organic solvents were combined and dried with anhydrous sodium sulfate.

Removal of the solvents and distillation of the residue gave the following fractions: (1) 0.8 g., b.p. 100-109° (0.2 mm.); forms a yellow precipitate with lead acetate, probably recovered dodecyl mercaptan; (2) 11.7 g. of a yellow liquid, b.p. 157-160° (0.2 mm.) and 161-165° (0.3 mm.); n_D^{20} 1.4739; (3) 5.8 g. of a yellow liquid, b.p. 158-161° (0.2 mm.); n_D^{20} 1.4740; (4) 1.6 g. of a yellow liquid, b.p. 155-160° (0.2 mm.); n_D^{20} 1.4750; (5) 5.6 g. of a yellowish-brown liquid, b.p. 152-217° (0.3 mm.), solidifying on cooling to a solid, melting at 48-49°. This product contained no nitrogen, but was not further identified.

The combined weights of fractions 2, 3, and 4 was 19.1 g. (58%).

Fractions 2, 3, and 4 were combined and distilled to give 17.9 g. (54%) of a yellow liquid, b.p. 151-152° (0.2 mm.); n_D^{20} 1.4739; d_{20}^{20} 0.9049; MR calcd., 103.4; found, 102.8.

Anal. Calcd. for $C_{21}H_{45}ONS$: S, 9.67. Found: S, 9.81 and 9.76.

Attempts to prepare the corresponding sulfoxide and sulfone by oxidation with hydrogen peroxide in acetic acid were unsuccessful.

2-Hydroxy-3-butenyl Dodecyl Sulfide. Sodium dodecyl mercaptide (0.1 mole) was prepared as described in the preceding experiment from 20.2 g. (0.1 mole) of dodecyl mercaptan and 2.3 g. (0.1 g. atom) of sodium in 150 ml. of toluene. To this refluxing solution was added dropwise a solution of 6.0 g. (0.085 mole) of 3,4-epoxybutene-1[171] in 25 ml. of toluene. The mixture was refluxed for six hours, during which time it became red.

The mixture was cooled, stirred with 100 ml. of water, the layers separated and the aqueous layer extracted with 100 ml. of benzene and 100 ml. of ether. The organic solvents were combined and dried over anhydrous sodium sulfate.

Removal of the solvents and distillation of the residue gave the following fractions: (1) 2.5 g., b.p. 84-97° (0.2 mm.); (2) 18.3 g. (77%) of a colorless liquid, b.p. 132-134° (0.1 mm.); n_D^{20} 1.4811; (3) 0.8 g., b.p. 131-141° (0.1 mm.); (4) 1.0 g., b.p. 160-175° (0.2 mm.).

Fraction 2 was redistilled to give an analytical sample, b.p. 135-137° (0.2 mm.); n_D^{20} 1.4802; d_{20}^{20} 0.9068; MR calcd. 85.12; found, 85.25. The product decolorizes bromine in carbon tetrachloride.

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[171] Kindly provided by Columbia Chemicals Division, Pittsburgh Plate Glass Company, Pittsburgh, Pa., and used without purification.

Anal. Calcd. for $C_{16}H_{32}OS$: S, 11.76. Found: S, 11.77 and 11.79.

This compound did not form an addition product with gold trichloride or platinum chloride.

2-Hydroxy-3-butenyl Hexadecyl Sulfide. Sodium hexadecyl mercaptide (0.05 mole) was prepared as previously described from 12.9 g. (0.05 mole) of hexadecyl mercaptan and 1.15 g. (0.05 g.) of sodium in 150 ml. of toluene. To this refluxing suspension was added dropwise a solution of 3.5 g. (0.05 mole) of 3,4-epoxybutene-1 in 25 ml. of toluene, all of the solid disappearing. The mixture was refluxed with stirring for five hours.

The solution was cooled, stirred with 100 ml. of water, the layers separated and the aqueous layer extracted with 100 ml. of ether. The organic solvents were combined and dried with anhydrous sodium sulfate.

Removal of the solvents and distillation gave the following fractions: (1) 0.8 g., b.p. 75-151° (0.15 mm.); (2) 7.0 g., b.p. 150-163° (0.15 mm.) solidifying on cooling to a white product, m.p. 25-26°; (3) 5.9 g., b.p. 163-164° (0.15 mm.); solidifying to white product, m.p. 26.5-27.5°; (4) 1.0 g., b.p. 159-165° (0.15 mm.); solidifying to white product, m.p. 27-27.5°. The combined weights of fractions 2, 3, and 4 was 13.9 g. (84%).

Anal. Calcd. for $C_{20}H_{40}OS$: S, 9.76. Found: S, 9.76 and 9.88.

2-Phenyl-2-hydroxyethyl Dodecyl Sulfide. Sodium dodecyl mercaptide (0.1 mole) was prepared as described in the preceding preparations from 20.2 g. (0.1 mole) of dodecyl mercaptan, and 2.3 g. (0.1 g. atom) of sodium in 150 ml. of toluene. To this refluxing solution was added dropwise a solution of 12.0 g. (0.1 mole) of styrene oxide[172] in 50 ml. of toluene, all of the solid disappearing. The solution was refluxed for five hours, forming a light brown solution. This product was worked up as described in the preceding experiments.

Distillation gave 28 g. of very light yellow material, distilling at 132-176° (0.1 mm.); n_D^{20} 1.5102. This product was redistilled through a 15 cm. Vigreaux column to give the following fractions: (1) 4.4 g., b.p. 102-178° (0.2 mm.); (2) 13.6 g., b.p. 178-180° (0.2 mm.); (3) 6.0 g., b.p. 181-182° (0.2 mm.). The combined weights of fractions 2 and 3 were 19.6 g. (61%).

Fraction 2, a colorless liquid, had the following constants: n_D^{20} 1.5130; d_{20}^{20} 0.9602; MR calcd., 100.5; found, 100.8.

Anal. Calcd. for $C_{20}H_{34}OS$: S, 9.96. Found: S, 9.87 and 10.05.

Attempts to prepare the methiodide[173] resulted in an oil and the 3,5-dinitrobenzoate melted at 34° after crystalliza-

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[172] This material was kindly furnished by Dow Chemical Company, Midland, Mich.

[173] Bost and Everett, *J. Am. Chem. Soc.*, 62, 1752 (1940).

tion from absolute ethanol. The naphthyl urethan melted above 200° after crystallization from carbon tetrachloride.

2-Phenyl-2-hydroxyethyl Hexadecyl Sulfide. Sodium hexadecyl mercaptide (0.05 mole) was prepared as previously described from 12.9 g. (0.05 mole) of hexadecyl mercaptan and 1.15 g. (0.05 g. atom) of sodium in 150 ml. of toluene. To this refluxing solution was added dropwise a solution of 6.0 g. (0.05 mole) of styrene oxide in 25 ml. of toluene, all of the material dissolving. The mixture was refluxed for five hours forming a light brown solution. This product was worked up as previously described.

Distillation gave the following fractions: (1) 1.3 g., b.p. 161-220° (0.3 mm.); (2) 2.3 g., b.p. 208-210° (0.3 mm.); n_D^{20} 1.5062; (3) 8.7 g., b.p. 220-221° (0.3 mm.); n_D^{20} 1.5070; d_{20}^{20} 0.9431; MR calcd., 118.9; found, 119.3; (4) 1 g., b.p. 177-192° (0.3 mm.). The combined weight of fractions 2 and 3 is 11.0 g. (58%).

Fraction 3 was analyzed.

Anal. Calcd. for $C_{24}H_{40}OS$: S, 8.47. Found: S, 8.35.

Phenacyl Dodecyl Sulfide. A solution of sodium ethoxide was prepared from 1.15 g. (0.05 g. atom) of sodium in 100 ml. of absolute ethanol. To this solution, in a nitrogen atmosphere, was added a solution of 10.1 g. (0.05 mole) of dodecyl mercaptan in 50 ml. of absolute ethanol, and the solution was refluxed for thirty minutes. A solution of 10.0 g. (0.05 mole) of phenacyl bromide in 35 ml. of absolute ethanol was added with stirring to the refluxing solution. The mixture was refluxed for six hours during which time salt formation was observed. The mixture was allowed to cool overnight.

After removal of the excess ethanol under reduced pressure 200 ml. of water was added to the residue, and the mixture was extracted with 400 ml. of ether in three portions. The ethereal extract was dried over anhydrous sodium sulfate.

Removal of the ether and distillation gave the following fractions: (1) 1.0 g., b.p. 50-89° (0.32 mm.); (2) 9.6 g., b.p. 174-178° (0.32 mm.), yellow liquid solidifying on cooling to a white solid, m.p. 32-4°; (3) 4.0 g., b.p. 178-180° (0.32 mm.); yellow liquid, solidifying to a white solid on cooling, m.p. 33-34°. The total yield of product melting 32-34° was 13.6 g. (85%).

An analytical sample was recrystallized from absolute ethanol and melted at 34-35°.

Anal. Calcd. for $C_{20}H_{30}OS$: S, 10.00. Found: S, 10.04 and 10.27.

Phenacyl Dodecyl Sulfide. This oxidation was carried out by the procedure of Inhoffen.[174] A mixture of 10 g. (0.028 mole) of 2-phenyl-2-hydroxyethyl dodecyl sulfide, 10.8 g. (0.05 mole) of aluminum isopropoxide (free from isopropanol), 82 ml. of anhydrous cyclohexanone and 500 ml. of toluene was refluxed with stirring for one hour. The mixture was hydrolyzed with dilute sulfuric acid, and the two layers were separated. The

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174. Inhoffen, Logeman, Hohlweg, and Serini, Ber., 71, 1032 (1938).

aqueous layer was extracted with ether, and the combined organic solvents were washed with sodium carbonate solution and water. The extracts were dried over anhydrous sodium sulfate.

Removal of the solvents and distillation of the residue gave 3.4 g. (34%) of liquid, b.p. 190-193° (0.2 mm.); solidifying to a white solid.

A 2,4-dinitrophenylhydrazone melted at 80-81° and a mixed melting point with an authentic specimen was not depressed.

Phenacyl Dodecyl Sulfide 2,4-Dinitrophenylhydrazone.[175] This compound, prepared by refluxing equal amounts of the ketone and 2,4-dinitrophenylhydrazine in absolute ethanol with the addition of a small amount of hydrochloric acid, melted at 80-81° after recrystallization from ethanol.

Anal. Calcd. for $C_{26}H_{36}O_4N_4S$: S, 6.40. Found: S, 6.22.

Tetradecylimido Tetradecyl Sulfide Hydrochloride.

Method 1.[138] A mixture of 4.5 g. (0.0215 mole) of myristonitrile[176] and 4.6 g. (0.02 mole) of tetradecyl mercaptan was dissolved in 50 ml. of anhydrous ether, and the ethereal solution was saturated with anhydrous hydrogen chloride. Crystallization did not occur. The mixture did not crystallize after

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[175] Shriner and Fuson, "The Systematic Identification of Organic Compounds", John Wiley and Sons, Inc., New York, N.Y., (1940) p. 143.

[176] This compound was obtained from Armour & Co. It was distilled and the fraction, b.p. 106-109° (0.1 mm.); n_D^{25} 1.440, was used in this preparation. Dorinson and Ralston, J. Am. Chem. Soc., 66, 361-2 (1944) gives the index of refraction of myristonitrile as n_D^{25} 1.440.

three days of standing in the ice-box. The ether was removed under reduced pressure, and the residue was washed with cold ether and dried to give 5.2 g. (55%) of white material, softening at 60°, melting at 65-68°.

Method 2.[138] A mixture of 4.5 g. (0.0215 mole) of myristonitrile and 4.6 g. (0.02 mole) of tetradecyl mercaptan was saturated with anhydrous hydrogen chloride. After thirty minutes precipitation occurred, and the mixture was allowed to stand in the ice-box for four hours. The product was washed with 125 ml. of cold anhydrous ether and dried for 12 hours over sulfuric acid under reduced pressure to give 6.2 g. (65%) of white product, softening at 60°, melting at 65-68°.

After four recrystallizations from anhydrous ether the product melted at 72-73°.

Anal. Calcd. for $C_{28}H_{58}NSCl$: S, 6.73; Cl, 7.47. Found: S, 6.32; Cl, 7.43.

1-Phenyl-1-chlorododecene-1. A mixture of 26.0 g. (0.1 mole) of laurophenone[177] and 20.8 g. (0.1 mole) of phosphorus pentachloride was slowly heated by means of an oil bath. At 100° all of the product dissolved and reaction ensued. The mixture was slowly heated to 150° and the temperature was maintained at 150-155° for two hours, during which time the mixture darkened. The mixture was allowed to cool.

The product was distilled under reduced pressure. After

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[177] This product was kindly furnished by L. F. Cason and melted at 42-44°.

distillation of the phosphorus oxychloride, the main body distilled at 140-156° (0.3 mm.) to give 24.5 g. (88%) of a slightly brown colored product; n_D^{20} 1.5138. The product was redistilled and boiled at 138-140° (0.3 mm.); n_D^{20} 1.5150; d_{20}^{20} 0.9647; MR calcd. 86.1; found 87.2.[178]

Anal. Calcd. for $C_{18}H_{27}Cl$: Cl, 12.73. Found: Cl, 12.98.

Dodecylmercuric Bromide. The directions of Meals[98] were followed in this preparation. Dodecylmagnesium bromide was prepared in 69 percent yield from 1.22 g. (0.05 g. atom) of magnesium and 12.5 g. (0.05 mole) of dodecyl bromide in 100 ml. of anhydrous ether. Reaction was slow in starting, but once reaction ensued, the reaction went normally. The product was filtered into a 500 ml. flask equipped with a Soxhlet extractor. In the Soxhlet bulb was placed 12.1 g. (0.0334 mole) of mercuric bromide, and the mixture was extracted for 24 hours. The mixture was then hydrolyzed with 10 g. of ammonium bromide in ice. The ether was distilled off, and the residue filtered, washed with water, a small amount of ethanol and then with ether. There was obtained 10.8 g. (71%) of white crystals melting at 108-110°. Meals obtained 54% melting at 108-108.7°.

o-Dodecylmercurimercaptobenzoic Acid. To a sodium ethoxide solution prepared from 0.5 g. (0.02 g. atom) of sodium in

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[178] Auwers, *Ber.*, *45*, 2801 (1912) found in substances of this structure  $C_6H_5-\overset{Cl}{C}=\overset{H}{C}-R$ an exaltation of 1.08. The above exaltation is 1.10.

100 ml. of 95 percent ethanol was added 1.54 g. (0.01 mole) of thiosalicylic acid.[179a] A white precipitate formed which dissolved on heating. To the hot solution was added a hot solution of 4.5 g. (0.01 mole) of dodecylmercuric bromide in 200 ml. of 95 percent ethanol, the mixture becoming clouded. A solution of one gram (0.04 g. atom) of sodium in 30 ml. of 95 percent ethanol was added, and the mixture refluxed with stirring for two hours and then stirred without heat for fourteen hours. A solid formed which settled out. The mixture was poured in 400 ml. of ether and extracted three times with 100 ml. portions of ether.

The aqueous layer was made acidic with hydrochloric acid, and a solid settled out. After standing for two hours, the solution was filtered to give 4.7 g. of a solid partially melting at 92°, melting with decomposition at 230-235°. This was recrystallized from 300 ml. of 95 percent ethanol to give 2.1 g. (47%) of recovered dodecylmercuric bromide (mixed m.p.) 110-111°.

Removal of the ethanol left 2.0 g. of a solid. This solid was extracted with 200 ml. of petroleum ether (b.p., 60-68°) to give 0.8 g. (15%) of cream-colored product, melting at 72°. The insoluble portion, 0.7 g. (45%), melted at 280-285° (dec.) and was assumed to be α-dithiosalicylic acid. α-Dithiosali-

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179. (a) This acid was purified as described in *Organic Syntheses, Coll. Vol. I*, (1944), 582, and melted at 163-164°; (b) Gattermann, *Ber.*, *32*, 1150 (1899).

cylic acid has been reported to melt at 239°.[179b]

Anal.[180] Calcd. for $C_{19}H_{30}O_2SHg$: Hg, 38.38; Neut. Equiv. 522. Found: Hg, 38.27; Neut. Equiv., 517.

This compound has been reported to melt at 70°.[141]

Picolinic Acid. Two hundred grams (2.15 moles) of α-picoline was added with stirring to a suspension of 340 g. (2.15 moles) of potassium permanganate in three liters of water. The mixture was heated on the steam bath, and after thirty minutes a vigorous reaction occurred which was controlled by immersing the reaction vessel in an ice-bath. The mixture was heated for one hour, and then a suspension of 170 g. (1.08 moles) of potassium permanganate in 500 ml. of water was added. The mixture was heated for another hour, followed by the addition of a third portion, 170 g. (1.08 moles), of potassium permanganate and 500 ml. of water. The mixture was heated for two hours. On cessation of stirring, the brown manganese dioxide settled out, leaving a colorless supernatant liquid.

The hot liquid was filtered, and the manganese dioxide washed with one liter of hot water. The hot mixture of filtrate and washings was made just acid to methyl red with 10 percent sulfuric acid, and to this hot solution was added a hot solution (80°) of 275 g. of copper sulfate pentahydrate in 500 ml. of water. The solution was stirred while cooling and then filtered.

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180. Tabern and Shelberg, J. Ind. Eng. Chem., Anal. Ed., 4, 401 (1932).

The blue copper picolinate was suspended in three liters of water, and hydrogen sulfide was passed in with stirring until on cessation of stirring the black copper sulfide settled, leaving a brown supernatant liquid. This precipitation required approximately three hours.

The mixture was filtered, and the filtrate was evaporated to dryness on the steam bath to give 170 g. of a brown solid, melting at 130-132°. The product was recrystallized from ethanol to give 131 g. (50%) of white crystals, melting at 135-136°. From the filtrate there was obtained 10 g. more of product, melting at 133-135°. The total yield of picolinic acid was 141 g. (52%).

Ethyl Picolinate. A suspension of 100 g. (0.81 mole) of picolinic acid in 700 ml. of absolute ethanol in a one-liter, three-necked, round-bottomed flask fitted with a stirrer, a condenser closed by a calcium chloride drying tube and a gas inlet tube fitted with a plunger[181] was cooled in an ice-bath and with good stirring was saturated with anhydrous hydrogen chloride. The ice bath was then removed, and the mixture refluxed for one hour with continuous passage of hydrogen chloride. The gas inlet tube was then removed, and the mixture refluxed for four and one-half hours, all of the solid going into solution.

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[181] Fieser, "Experiments in Organic Chemistry", Heath and Company, New York, N.Y., (1941), Part II, p. 310.

The excess ethanol was removed under reduced pressure on the steam bath, and the residue poured into the minimum amount of excess saturated sodium carbonate solution. The solution was extracted with 700 ml. of ether in three portions, and the ethereal extracts were combined and dried over anhydrous sodium sulfate.

The ether was removed by distillation, and the residue distilled to give 90 g. (73%) of a colorless liquid, distilling at 135-136° (18 mm.).

From the basic aqueous extract, subsequent to acidification with 10 percent sulfuric acid and precipitation with hot copper sulfate solution, there was obtained 15.5 g. (12%) of copper picolinate.

Methyl 2-Pyridyl Ketone.[182] A suspension of 1.2 moles of sodium ethoxide in 1100 ml. of anhydrous thiophene free benzene was prepared from 27.6 g. (1.2 g. atoms) of sodium sand and 55.2 g. (1.2 moles) of absolute ethanol. To this warm mixture there was added with vigorous stirring a mixture of 120.8 g. (0.8 mole) of ethyl picolinate and 140.8 g. (1.6 moles) of anhydrous ethyl acetate at such a rate as to cause gentle reflux. During the addition the sodium ethoxide disappeared, the mixture becoming clear and then settling to a thick yellow mush.

This mixture was refluxed with stirring for twelve hours,

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182. Gilman, Tolman, and Massie, J. Am. Chem. Soc., 68, 000 (1946).

cooled and poured into a cold solution of 40 g. of sodium hydroxide in 800 ml. of water. The light yellow solid was filtered off, and after the addition of 800 ml. of water to the filtrate, the benzene and aqueous layers were separated. The benzene layer was extracted with 400 ml. of water, and the combined aqueous layers were extracted with 100 ml. of benzene.

The aqueous layer was then acidified with concentrated hydrochloric acid; the yellow precipitate was suspended in the solution; and the mixture was acidified with concentrated hydrochloric acid, 350 ml. of acid being added in all. The total volume of solution was approximately two and one-half liters.

The solution was refluxed for two hours, cooled, made basic with solid sodium carbonate and extracted with 1500 ml. of ether in portions. The combined ethereal extracts were dried over anhydrous sodium sulfate.

The ether was distilled off, and the residue distilled at 79-80° (10 mm.) to give 72 g. (75%) of a colorless liquid; n_D^{20} 1.5200.

2-(2'-Pyridyl)cinchoninic Acid. This preparation was adapted from the method of Lindwall.[183] To a solution of 40 g. (0.27 mole) of isatin in 160 g. of 25 percent potassium hydroxide solution was added a solution of 34 g. (0.29 mole) of methyl 2-pyridyl ketone in 250 ml. of 95 percent ethanol. The

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[183] Lindwall, Bandes, and Weinberg, ibid, 53, 317 (1931).

mixture was refluxed for twelve hours.

The excess ethanol was removed under reduced pressure, and the solid residue was dissolved in 1000 ml. of water. The resulting solution was extracted with 400 ml. of ether in two portions. The aqueous extract was acidified with vigorous stirring by 100 ml. of 50 percent acetic acid. The precipitate was filtered, redissolved in a solution of 40 g. of potassium hydroxide in 600 ml. of water and reprecipitated by 100 ml. of 50 percent acetic acid.

The precipitate was filtered, washed with water, warmed for fifteen minutes with 400 ml. of 95 percent ethanol, chilled and filtered to give 55 g. (81%) of a white product, melting with decomposition at 302-303°. A sample was purified for analysis by refluxing with Norite a solution of the material in potassium hydroxide, filtration and acidification with 50 percent acetic acid. The purified sample melted at 302-303°.

Anal. Calcd. for $C_{15}H_{10}O_2N_2$: N, 11.20. Found: N, 11.01.

Ethyl 2-(2'-Pyridyl)cinchoninate. A mixture of 50 g. (0.2 mole) of 2-(2'-pyridyl)cinchoninic acid, 500 ml. of absolute ethanol and 90 ml. of concentrated sulfuric acid was refluxed for eight hours, all of the material going into solution. The excess ethanol was removed under reduced pressure, and the residue was poured over 500 g. of ice water. The solution was made alkaline with solid sodium carbonate. The product crystallized immediately and was filtered and dried.

The crude material was recrystallized from 50 percent ethanol with the addition of Norite to give 47 g. (85%) of white crystals, melting at 70-71°. A sample purified for analysis melted at 71-72° after three recrystallizations from 50 percent ethanol. The compound had the same melting point when recrystallized from petroleum ether (b.p., 60-68°).

Anal. Calcd. for $C_{17}H_{14}O_2N_2$: N, 10.09. Found: N, 10.38.

2-Nitropiperonal. 2-Nitropiperonal was prepared by the nitration of piperonal following the method of Salway[184] in yields of 68 and 72 percent, with sides yields of 14 percent of 3,4-methylenedioxynitrobenzene. This compound was also obtained in 77 percent yield by the method of Parys[185] with a yield of 14 percent of 3,4-methylenedioxynitrobenzene. The former method used concentrated nitric alone as the nitrating agent; whereas, the latter method used a mixture of concentrated nitric acid and glacial acetic acid.

5,5',6,6'-Dimethylenedioxyindigotin-(Piperonalindigo). This compound was prepared in yields of 47-63 percent by the method of Jones and Robinson[186] by adding a solution of 2-nitropiperonal in acetone to a one normal potassium hydroxide solution and in 58 and 65 percent yields by the method of Tan-

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184. Salway, J. Chem. Soc., 95, 1163 (1909).
185. Parys, Rec. trav. chim., 49, 20 (1930).
186. Jones and Robinson, J. Chem. Soc., 111, 915 (1917).

asescu and Georgescu.[187] This latter method involves the formation of the addition product from 2-nitropiperonal and acetone using sodium phosphate as the condensing agent followed by ring closure with 10 percent sodium hydroxide solution.

3,4-Methylenedioxyisatin. Considerable difficulty was encountered in this step which involved oxidation of the indigo to the isatin. The method of Rabinovich and Dzirkal,[188] which used sodium dichromate and sulfuric acid as the oxidizing agent, gave yields of 14-41 percent of the isatin derivative with recoveries of 44-54 percent of piperonalindigo. The use of sodium dichromate and nitric acid[189] gave yields of 20-35 percent of the oxidation product with recoveries of 48-64 percent of starting material, and nitric acid and chromium trioxide[190] gave yields of 14-54 percent with recoveries of 24-44 percent of piperonalindigo. Potassium permanganate and sulfuric acid gave a 10 percent yield of 3,4-methylenedioxyisatin and 65 percent of starting material. These products were rather crude, and attempts to purify them were unsuccessful.

The synthesis of this compound by the method of Robinson

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[187] Tanasescu and Georgescu, Bull. soc. chim., [4], 51, 234 (1932).

[188] Rabinovich and Dxirkal, Khim. Farm. Prom., 190 (1933) [C.A., 28, 475 (1934)].

[189] Henessey, J. Soc. Dyers and Colourists, 53, 347 (1937).

[190] Private communication from the laboratories of Columbia University, New York, N.Y.

and Robinson,[191] in which 2-nitropiperonal is converted to the cyanohydrin, subsequent to hydrolysis to 2-nitro-3,4-methylenedioxymandelic acid, which is then reduced by ferrous sulfate and ammonium hydroxide to 3,4-methylenedioxyisatin, was attempted. A 46 percent yield of the mandelic acid, melting six degrees low was obtained, but the oxidation of this material was unsuccessful.

<u>6,7-Methylenedioxy-2-phenylcinchoninic Acid</u>.[190] A mixture of 5 g. (0.089 mole) of potassium hydroxide, 15 ml. of water, 5.7 g. (0.047 mole) of acetophenone and 6 g. (0.031 mole) of crude 3,4-methylenedioxyisatin was refluxed for eight hours on the water bath.

The dark brown homogeneous liquid was then diluted with 50 ml. of water, and this solution was extracted with 200 ml. of ether in three portions to remove the excess acetophenone. The aqueous layer was then acidified with 11 ml. of 50 percent acetic acid, a dark yellowish-brown precipitate settling out of the reaction mixture. Filtration and drying gave five grams of material.

This crude product was then purified by solution in 30 ml. of 10 percent sodium hydroxide solution with the addition of 20 g. of sodium chloride and 50 ml. of water. The mixture was heated, chilled and filtered. The precipitate was dissolved in 75 ml. of water, heated with Norite, filtered and

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[191] Robinson and Robinson, J. Chem. Soc., 105, 1466 (1914).

acidified with acetic acid. Filtration and drying gave 2 g. (22%) of a yellow product melting at 225-250°.

3,4-Methylenedioxyaniline. A suspension of 81 g. (0.48 mole) of 3,4-methylenedioxynitrobenzene in 400 ml. of absolute ethanol and a teaspoon of Raney nickel catalyst was heated to reflux and shaken under 60 pounds of pressure of hydrogen. Reduction required two hours, as shown by the approximate intake of the theoretical amount of hydrogen.

The catalyst was removed by filtration, and the ethanol removed by vacuum distillation in a nitrogen atmosphere. The residue was distilled in a nitrogen atmosphere to give 60 g. (90%) of a colorless liquid, b.p. 97° (0.2 mm.). This product solidified on cooling.

This compound has been prepared by the Hofmann reaction on piperonylic amide.[192] The boiling point was reported as 144° (16 mm.).

3,4-Methylenedioxy-N-benzylideneaniline. This procedure was adapted from the directions of Bigelow and Eatough[193] for the preparation of N-benzylideneaniline. To 39 g. (0.36 mole) of freshly distilled benzaldehyde was added with vigorous stirring 50 g. (0.36 mole) of 3,4-methylenedioxyaniline. Reaction was immediate and vigorous, and the mixture became cloudy and warm. The mixture was stirred for fifteen minutes

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192. Rupe and von Majeski, Ber., 33, 3407 (1900).

193. Bigelow and Eatough, Organic Syntheses, Coll. Vol. I, 80 (1944).

and then poured with vigorous stirring into 60 cc. of 95 percent ethanol and stirred for ten minutes. The mixture was placed in the icebox for twelve hours, and crystallization occurred. The mixture was filtered and dried to give 79 g. (96%) of a yellowish-brown solid, melting at 49-50°. A sample purified for analysis by recrystallization from aqueous ethanol separated as yellow needles, melting at 49.5°-50.5°.

Anal. Calcd. for $C_{14}H_{11}O_2N$: N, 6.22. Found: N, 6.57.

6,7-Methylenedioxy-2-phenylcinchoninic Acid. This preparation followed essentially the directions of Chaminitus[194] for 2-phenylcinchoninic acid. To a refluxing solution of 72 g. (0.32 mole) of 3,4-methylenedioxy-N-benzylideneaniline in 300 ml. of methanol was added dropwise 27 g. (0.31 mole) of pyruvic acid. Crystallization occurred just before the completion of the addition. The mixture was refluxed for forty-five minutes and allowed to cool.

The mass was filtered, and the precipitate washed with cold methanol. The solid was dissolved in a solution of 40 g. of sodium hydroxide in 1000 ml. of water. Acidification of the solution with 50 percent acetic acid, filtration and drying gave 45 g. (48%) of a yellow product, softening at 240°, melting at 242-248°.

The compound was purified for analysis by boiling a solution of the compound in 10 percent sodium hydroxide solution

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194. Chaminitus, Pharm. Zentralhalle, 69, 550 (1928).

with Norite. This mixture was filtered and acidified with 50 percent acetic acid. The compound melted at 250-252° on rapid heating if the sample was added to the melting block at a temperature of 230°, while if the sample was added at a lower temperature with slow heating, the product sublimed at approximately 225°.

Anal. Calcd. for $C_{17}H_{11}O_4N$: N, 4.78. Found: N, 4.57.

Methyl 6,7-methylenedioxy-2-phenylcinchoninate. One gram (0.0034 mole) of 6,7-methylenedioxy-2-phenylcinchoninic acid was suspended in 200 ml. of absolute methanol, and anhydrous hydrogen chloride was passed in for fifteen minutes. The mixture became warm and was allowed to stand for four hours, crystals separating on cooling.

The mass was poured into excess sodium bicarbonate solution with good stirring and allowed to stand for twelve hours. Filtration and recrystallization from methanol gave 1.04 g. (quantitative) of yellow needles, melting at 132-133°.

The crude acid (m.p. 225-250°) obtained from 3,4-methylenedioxyisatin was esterified as described above. Extraction by methanol of the dark precipitate obtained, refluxing of the methanol solution with Norite, filtration and cooling, gave crystals melting at 132-133°. This product showed no depression in melting point when mixed with a sample of the ester described above.

Anal. Calcd. for $C_{18}H_{13}O_4N$: N, 4.56. Found: N, 4.69.

1-Diethylamino-4-benzylideneaminopentane.[195] A mixture of 15.8 g. (0.2 mole) of 1-diethylamino-4-aminopentane[196] and 10.6 g. (0.1 mole) of freshly distilled benzaldehyde in 25 ml. of anhydrous benzene was shaken for ten minutes and the mixture became warm and turbid. The mixture was allowed to stand for ten hours during which time water separated.

The water layer was removed, and the benzene layer dried over anhydrous sodium sulfate. Removal of the solvent by distillation and fractionation of the residue gave 16.4 g. (67%) of a colorless liquid; b.p. 148-150° (2.5 mm.); n_D^{20} 1.5134; d_{20}^{20} 0.9087.

Anal. Calcd. for $C_{16}H_{26}N$: N, 11.38. Found: N, 11.36.

1-Diethylamino-4-o-chlorobenzylideneaminopentane.[195] A mixture of 7.9 g. (0.05 mole) of 1-diethylamino-4-aminopentane and 7 g. of *o*-chlorobenzaldehyde in 25 ml. of benzene was shaken for thirty minutes and the mixture became warm and turbid. The mixture was allowed to stand for ten hours during which time water separated.

The water layer was removed, and the benzene layer dried over anhydrous sodium sulfate. Removal of the solvent by distillation and fractionation of the residue gave 9.3 g. (71.5%) of a yellow liquid; b.p. 150-151° (3.0 mm.); n_D^{20} 1.5225; d_{20}^{20} 0.9989.

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[195] Gilman and Massie, *J. Am. Chem. Soc.*, *68*, 908 (1946).

[196] Kindly supplied by Parke-Davis and Company, Detroit, Michigan.

Anal. Calcd. for $C_{16}H_{25}NCl$: N, 10.00. Found: N, 10.17.

1-Diethylamino-4-o-methoxybenzylideneaminopentane.[195] A mixture of 7.9 g. (0.05 mole) of 1-diethylamino-4-aminopentane and 6.8 g. (0.05 mole) of o-methoxybenzaldehyde in 25 ml. of benzene was shaken for thirty minutes and allowed to stand for ten hours. The mixture was worked up as described in the two previous preparations.

Distillation of the residue gave 11 g. (80%) of a yellow liquid; b.p. 154-155° (3.0 mm.); n_D^{20} 1.5210; d_{20}^{20} 0.9558.

Anal. Calcd. for $C_{17}H_{28}ON$: N, 10.14. Found: N, 10.38.

1-Diethylamino-4-p-methoxybenzylideneaminopentane.[195] A mixture of 7.9 g. (0.05 mole) of 1-diethylamino-4-aminopentane and 6.8 g. (0.05 mole) of *p*-methoxybenzaldehyde in 25 ml. of benzene was shaken for thirty minutes. It was necessary to warm the mixture to initiate reaction. The mixture was allowed to stand for twelve hours and then was worked up as described in the preceding preparations.

Distillation of the residue gave 10.5 g. (76%) of a yellow liquid; b.p. 153-154° (3.0 mm.); n_D^{20} 1.5250; d_{20}^{20} 0.9584.

Anal. Calcd. for $C_{17}H_{28}ON$: N, 10.14. Found: N, 10.32.

1-Diethylamino-4-p-dimethylaminobenzylideneaminopentane.[195] A mixture of 7.9 g. (0.5 mole) of 1-diethylamino-4-aminopentane and 7.5 g. (0.05 mole) of *p*-dimethylaminobenzaldehyde in 25 ml. of benzene was warmed on a steam bath until solution was complete and allowed to stand for twelve hours. The mixture was worked up as previously described.

Distillation of the residue gave 9.3 g. (64%) of a yellow liquid; b.p. 193-194° (3.0 mm.); n_D^{20} 1.5580; d_{20}^{20} 0.9450.

Anal. Calcd. for $C_{18}H_{31}N_3$: N, 14.53. Found: N, 14.54.

Phenothiazine. This material was prepared by the general method in which diphenylamine and sulfur are heated together in the presence of iodine as a catalyst.[115] The yields were quantitative.

(?),(?)-Diacetylphenothiazine. To a suspension of 53.2 g. (0.04 mole) of anhydrous aluminum chloride in 175 ml. of dry carbon disulfide was added slowly 19.9 g. (0.1 mole) of phenothiazine, the mixture turning red. Twenty and four-tenths grams (0.2 mole) of acetic anhydride was then added, hydrogen chloride gas being given off as the reaction proceeded. The mixture was stirred for four hours and then poured into a beaker of ice water, a thick pasty mass forming. The mixture was then treated with hydrochloric acid and benzene and allowed to stand for twelve hours during which time a yellow solid (9.1 g.), melting at 229-230° separated. This solid was extracted in a Soxhlet extractor with acetone, and 5 g. (18%) of orange crystals, melting at 252-253° was obtained.

Removal of the benzene left a waxy substance from which 6 g. (25%) of N-acetylphenothiazine (identified by mixed m.p.) was obtained. No other identifiable products were obtained.

The orange product was recrystallized from acetone, using Norite. The purified product melted at 253-254°.

Anal. Calcd. for $C_{16}H_{13}O_2NS$: N, 4.94. Found: N, 5.14.

The positions of the acetyl groups were not determined, but it was shown that neither one was on the nitrogen atom as evidenced by lack of hydrolysis with either ethanolic sodium hydroxide or ethanolic hydrogen chloride.

Dibutylformamide. This compound was prepared by the method of Fieser and Jones.[197] A mixture of 130 g. (1 mole) of dibutylamine, 100 g. (1.9 mole) of 87-90 percent formic acid and 600 ml. of toluene was slowly distilled through a 24-inch Vigreaux column over a period of one and one-half hours until 500 ml. of liquid distilled. The temperature of distillation at the beginning was 87-88°, and at the end it was 108-110°.

The residue was distilled at 11 mm. and the fraction distilling at 111-134° was collected, n_D^{20} 1.4441. Redistillation gave 145 g. (92%) of a colorless liquid; b.p. 76-78° (0.25 mm.); n_D^{20} 1.4435; d_{20}^{20} 0.8932.

Anal. Calcd. for $C_9H_{19}ON$: N, 8.92. Found: N, 8.83.

N-Bromosuccinimide. This compound was prepared by the method of Ziegler[198] from succinimide and bromine in sodium hydroxide solution. The product was analyzed by iodometric titration. It was highly essential that the material be of the highest purity, as less pure material required longer heating and gave lower yields in the subsequent preparation.

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[197] Fieser and Jones, Organic Syntheses, 20, 66 (1940).

Ethyl γ-Bromocrotonate. This preparation followed essentially the directions of Ziegler[198] for the corresponding methyl ester. A mixture of 133 g. (1.0 mole) of 98 percent N-bromosuccinimide, 228 g. (2 moles) of ethyl crotonate[199] and 300 ml. of anhydrous carbon tetrachloride was refluxed for six hours, succinimide precipitating. The completion of the reaction was noted in two ways: (1) the mixture turned brown; (2) the mixture no longer liberated iodine from acidified potassium iodide solution.

The succinimide was filtered off and washed with 100 ml. of cold carbon tetrachloride to give, subsequent to drying, 93 g. (94%) of recovered succinimide. The carbon tetrachloride was removed by distillation at atmospheric pressure, and the excess ethyl crotonate was removed by distillation under reduced pressure.

Distillation of the residue at 66-67° (0.3 mm.) gave 158 g. (82%) of material; n_D^{16} 1.492. The compound has been reported[200] to distill at 97-98° (15 mm.); n_D^{16} 1.490.

3-Diethylamino-2-hydroxybutyronitrile.[201] *(Method A)* A cooled mixture of 185 ml. of concentrated hydrochloric acid in

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[198] Ziegler, Späth, Schaaf, Schuman, and Winkelmann, *Ann*., *552*, 108 (1942).

[199] Michael, *Ber*., *33*, 3766 (1900).

[200] Rambaud, *Bull. soc. chim*., [5], *1*, 1343 (1934).

[201] Unpublished work of C. S. Sherman and L. Goldman, N.D.R.C. report.

200 ml. of 95 percent ethanol was added with vigorous stirring to a solution of 279 g. (2.16 moles) of 1-diethylamino-2,3-epoxypropane in 200 ml. of 95% ethanol, which was cooled by an ice-bath. The internal temperature was not allowed to rise above 25°. To the resulting solution was added 148 g. (2.16 moles) of powdered potassium cyanide (95%). The ice-bath was removed, and the flask was heated by means of a water bath to 65-70° at which temperature it was maintained for an hour. The reaction temperature was then raised to 85°, and the mixture gently refluxed for five hours. The mixture was allowed to cool to room temperature with stirring. The solid material was filtered off by suction and washed with acetone until colorless. The acetone washings were added to the original filtrate, and the mixture filtered again. The acetone and ethanol were removed at atmospheric pressure until the distilling vapors reached a temperature of 92°. Fractionation under reduced pressure gave 191 g. (57%) of a colorless liquid, distilling at 108-114° (2 mm.); n_D^{25} 1.4516.

<u>3-Diethylamino-2-hydroxybutyronitrile. (Method B)</u> A mixture of 111 g. (1.2 moles) of epichlorohydrin, 86.5 g. (1.18 moles) of diethylamine and 3.6 ml. of water was stirred at 25-30° for five and one-half hours. To the resulting solution was added with stirring 200 ml. of 95 percent ethanol, 56 ml. of water and 78 g. (1.12 moles) of potassium cyanide (95%). After 20 minutes the temperature rose to 65°, where it

was kept for four hours. The mixture was then worked up as described in Method A. Distillation gave 115 g. (62%) of a colorless liquid, distilling at 99-100° (0.6 mm.); $n_D^{26.5}$ 1.4510.

IV. DISCUSSION

A. Methods of Testing

Most of these compounds were tested for their therapeutic activity by Dr. Guy P. Youmans, Northwestern University Medical School, Chicago, Illinois. The pharmacological results given in this thesis are still restricted and are given here only to illustrate the physiological effects of the agents prepared.

The earlier emphasis in these investigations was on antimalarial agents. The method of testing these compounds in avian malaria has been thoroughly discussed by Tolman.[16] The later emphasis was chiefly on antituberculous agents. These were tested _in vitro_ against tubercle bacilli. These compounds were also tested for other physiological properties, and these results are also given.

B. High-Molecular Weight Nitrogen Compounds

Tertiary Amines

The presence of the tertiary amino group in many effective therapeutic agents made it desirable to prepare and examine a series of simple tertiary amines for physiological activity.

Derivatives of dibutylamine were chosen for the following reasons: (a) dibutylamine is relatively inexpensive; (b) derivatives of dibutylamine up to the C_{10} alkyl group are known, and the results obtained would aid the study of homology; (c) the volatility of dibutylamine was of such a nature as to facilitate the purification of the reaction products and yet permit the use of a relatively high reaction temperature. The entire series of even-numbered derivatives were desired as it is known that physiological properties may recur in a series.

The dibutylalkylamines from C_{12} to C_{18} were prepared in good yields by the condensation of two molar equivalents of dibutylamine and one molar equivalent of the alkyl bromide.

No report has been received as yet on the physiological activity of these compounds.

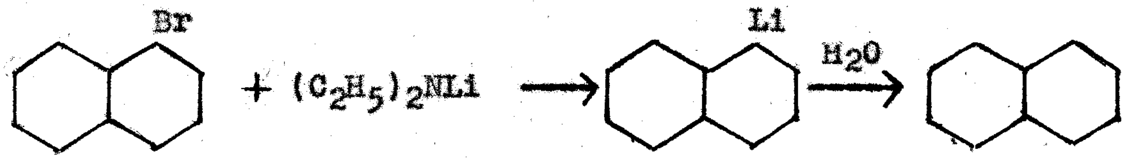
The unavailability of the odd-numbered alkyl bromides made another method for their preparation necessary. Dibutylaminomethyl butyl ether was cleaved by dodecylmagnesium bromide to give dibutyltridecylamine. The cleavage occurred in 52 percent yield and thus showed that this useful reaction can be extended to high-molecular weight organometallic compounds. No report on the therapeutic activity of this compound has been received. The small amount of variance in the indices of refraction (1.4471-1.4513) of these compounds is quite interesting.

It was desirable to test the activity of a tertiary amine, where all three alkyl groups were high-molecular weight groups. Trioctadecylamine was prepared by the procedure of Hoyt.[60] In the preparation of octadecyl chloride, the effect of the purity of the thionyl chloride was quite significant. In the preparation of acyl chlorides, the purity of the thionyl chloride is not too important, but for alkyl chlorides very pure material is necessary.

The activity of trioctadecylamine against tubercle bacilli *in vitro* was >10 (base 2.5).

Tertiary Amines from Molecular Rearrangements

The reaction of *α*-halogenonaphthalenes with lithium diethylamide to give *β*-diethylaminonaphthalene has been described. The presence of the naphthalene indicated the possibility of halogen-metal interconversion being a side-reaction during the rearrangement, but no *α*-naphthoic acid could be isolated and



identified. *β*-Diethylaminonaphthalene had an activity of 5.0 (base 2.5) against tubercle bacilli *in vitro*.

Kyle[126] found that lithium dibutylamide gave a better yield than lithium diethylamide. A logical extension of this reaction was the reaction of lithium didodecylamide with *α*-bromonaphthalene. Rearrangement was found to occur in better yield although the high boiling point of β-didodecylaminonaphthalene made purification difficult. The melting point of the hydrochloride could not be raised to the melting point of the authentic specimen, but a mixed melting point was not depressed and lay between the two samples. Similarly the observations of Hickinbottom and Lambert,[158] that the di-high-molecular weight alkyl anilines did not form picrates, was confirmed. The use of other methods of identification such as the formation of addition products or coupling were also unsuccessful. The non-polar solvent effect of these groups was noticeable in the ether solubility of the hydrochloride. A report of the therapeutic activity of this hydrochloride has not been received.

Three moles of β-naphthylamine and one mole of dodecyl bromide in ethanol gave an 83 percent yield of β-N-dodecylaminonaphthalene, thus substantiating the generalization that where an excess of amine can be used, very good yields of alkylated amines are obtained. However, unavailability of some amines and physical properties which make separation of the excess amine difficult make other methods of synthesis desirable. The use of metallic derivatives of amines where rearrangement does not take place seems to be worthy of further study. This method was not further investigated in this study.

β-N-Dodecylaminonaphthalene and dodecyl bromide were reacted to give 37 percent of β-didodecylaminonaphthalene. Again the high boiling point made purification of the product difficult.

Another interesting variation was the reaction of *o*-chlorophenyl dodecyl ether with lithium diethylamide. Kyle[202] found that the use of *o*-chlorophenetole gave a yield of 38% of the *meta* amine as compared with 35% of *m*-diethylaminoanisole under the same conditions. However, after twenty-four hours reaction time no evidence of reaction between *o*-chlorophenyl dodecyl ether and lithium diethylamide was obtained. This is in line with the observation of Cason[203] who found that *o*-chlorophenyl dodecyl ether and sodamide in liquid ammonia would not react and that the use of the high pressure conditions of a bomb was necessary to cause reaction and subsequent rearrangement. This possibility, however, was not investigated with *o*-chlorophenyl dodecyl ether.

Derivatives of Amines

Compounds of the C_{14} (tetradecyl) and C_{16} (hexadecyl) series seemed especially promising as therapeutic agents. Drea[48] has given the importance of the C_{14} and C_{16} chains against human tubercle bacilli, and the studies on quaternary ammonium salts have further emphasized the pharmacological importance of the C_{16} chain. Adams and his group,[61] in their studies on leprosy bacilli, found 16 carbons to be the optimum

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[202] Unpublished studies of R. H. Kyle.

[203] Unpublished work of L. F. Cason.

number of carbon atoms.

The need for derivatives of high-molecular weight aliphatic amines has been emphasized by Hoyt,[60] Harber[119] and Hunter.[204] These workers prepared derivatives of dodecyl- and octadecylamines but not tetradecyl- and hexadecylamines. These investigators used as derivatizing reactions: (a) the condensation of amines and carboxylic or sulfonic acids to form ammonium salts or amides; (b) the reaction of amines and acid derivatives to give amides, and (c) the formation of urea and thiourea derivatives.

These pharmacological and chemical considerations initiated the preparation of derivatives of tetradecyl- and hexadecylamines.

In the preparation of suitable derivatives for high-molecular weight amines, Harber[119] emphasized the necessity of using pure starting materials. He stated, "In high-molecular weight aliphatic chemistry the rule holds that to prepare pure compounds one must start with pure compounds. This is because the impurities are usually also of high-molecular weight and, in general, have the same physical properties". The finding of Harber that the use of pure amines gave sharp melting derivatives was substantiated.

The preparation[119] of high-molecular weight amine hydrochlorides by the use of absolute ethanol and hydrochloric acid

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[204] Hunter, B.A., Doctoral Dissertation, Iowa State College (1940).

was found to be very satisfactory, tetradecylamine hydrochloride being obtained in 90 percent yield and hexadecylamine hydrochloride in quantitative yield. Against tubercle bacilli *in vitro*, tetradecylamine hydrochloride had an activity equal to that of 4,4'-diaminodiphenylsulfone [2.5, base (2.5)], while hexadecylamine hydrochloride had an activity of 10.0 (base 2.5). This remarkable difference in activity suggested the preparation and testing of dodecylamine hydrochloride, but reports on the activity of this compound have not been received.

The preparation of the ureas from the amines and potassium cyanate proceeded in good yield with ease. Likewise the reaction of the amines and carbon disulfide gave the thioureas in good yield. Although these ureas had been previously prepared by another method[117] and dihexadecyl-thiourea was known,[133] no tuberculostatic activity of these compounds has been given. Ditetradecylthiourea showed an activity against tubercle bacilli of 10.0 (base 2.5), and dihexadecylthiourea showed an activity of >10 (base 2.5). Again the greater activity of the C_{14} derivative was noticeable. No report has been received on tetradecyl-urea, but the tuberculostatic activity of hexadecylurea was 10.0 (base 2.5).

The phenylthioureas were easily prepared from phenyl isothiocyanate and the amines. The therapeutic activity of the CNS group initiated the preparation of these compounds. No report has been received on the tetradecyl compound, and the tuberculostatic activity of N-phenyl-N'-hexadecyl thiourea was >10 (base 2.5).

The oxalamides formed very easily and were easily purified. The tetradecyl compound had an activity against tubercle bacilli of >10 (base 2.5) while hexadecyl-oxalamide had an activity of 10 (base 2.5). In this case the hexadecyl derivative appeared to be more active.

The benzenesulfonamides proved to be easily formed and easily purified. No reports on their therapeutic activity have been received.

Thus, none of these derivatives shows promise as therapeutic agents against tuberculosis.

Table I

Melting Points of Amine Derivatives

<u>Derivative</u>	C_{12}	C_{14} [a]	C_{16} [a]
Urea	107° [d]	112-113°	106-107°
Dithiourea	74.5-75° [b]	80-81°	87-88°
Phenyl-thiourea	69.5-69.8° [b]	77.5-78.0°	82-82.5°
Oxalamide	120-121° [c]	118-119°	119-120°
Benzene-sulfonamide	58.0-58.5° [b]	66-67°	71-72°

Table I (Continued)

Derivative	(Mixed C_{14} & C_{16})[a]	C_{18}
Urea	104-105°	112.5-113° [b]
Dithiourea	78-79°	95.2-96.0° [b]
Phenyl-thiourea	75-76.5°	86-87° [b]
Oxalamide	115-116°	119-119.5° [b]
Benzene-sulfonamide	62-64°	77-77.5° [b]

Although these derivatives were easily prepared in good yields, their melting points (Table I) are so close that they are not too valuable for distinguishing the tetradecyl from the hexadecyl derivatives. The small depressions of the mixed melting points from the melting point of the tetradecyl derivative and the narrow melting range of the mixed melting points is quite noticeable. The oxalamides melt remarkably close and the reverse melting point order of the ureas is of interest. Of the derivatives prepared in this investigation, the benzenesulfonamides appear to be best. They melt five degrees apart and a mixture of the two (C_{14} and C_{16}) gives a four degree depression. Other derivatives may prove more valuable in the above respect, but as the chief interest of this thesis was in therapeutic activity, no further studies were made.

(a) prepared in these investigations; (b) ref. 119; (c) Grunfeld, *Compt. rend*, **194**, 893 (1932); (d) ref. 117.

C. High-Molecular Weight Sulfur Compounds

Quinoline Sulfides

The quinoline ethers, especially the 6-methoxy derivatives, have proved to be very good antimalarial agents. Plasmoquin, quinine and atebrin, the three most effective antimalarials, are 6-methoxyquinoline derivatives. In anti-tuberculous studies[23b] the ether linkage was found to be of some value. The replacement of oxygen by sulfur in some aromatic phenols has been found[205] to increase the bactericidal action against B. typhosus and Staph. aureus. These considerations made worthy the investigation of quinoline sulfides as therapeutic agents.

A series of 6-quinolyl dodecyl sulfides was prepared. 5-Nitro-6-chloroquinoline and sodium alkyl mercaptides at room temperature gave good yields of the 5-nitro-6-quinolyl alkyl sulfides. The effect of temperature in this condensation was quite noticeable. When the addition was made at the reflux temperature of methyl cellosolve, only a small amount of product was obtained, but if the reactants were allowed to stir at room temperature for at least two hours, the mixture could then be heated. Benkeser[206] observed similar results with 7-nitro-8-chloroquinoline and sodium methyl mercaptide.

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[205] (a) Hilbert and Johnson, J. Am. Chem. Soc., 51, 1526 (1929); (b) Dunning, Dunning, and Drake, ibid, 53, 3466 (1931); (c) Klormann, Gates, and Shternov, ibid, 54, 1204 (1932); (d) Suter and Hansen, ibid, 54, 4100 (1932).

[206] Unpublished work of R. A. Benkeser.

5-Nitro-6-quinolyl dodecyl sulfide was reduced to 5-amino-6-quinolyl dodecyl sulfide with Raney nickel[164] in the usual manner. This amino group proved quite unreactive. It could not be condensed with salicylaldehyde nor acetonylacetone. The amine could not be condensed with 5-isopropylaminopentyl chloride hydrochloride either with forty-eight hours of refluxing in ethanol or by heating the two components without a solvent. The acetamido derivative, however, was successfully prepared.

8-Acetamido-6-chloro-5-nitroquinoline was condensed with sodium alkyl mercaptides.[168] This acetamido group was very easily hydrolyzed, and with both the methyl and the dodecyl compounds, the amino, rather than the acetamido compound, was obtained. The higher melting point and the greater insolubility of the amino derivative was also quite striking. In these condensations the temperature of addition had no effect.

8-Amino-5-nitro-6-quinolyl dodecyl sulfide was acetylated using acetic anhydride and acetic acid. Reduction of this acetylated compound to 8-acetamido-5-amino-6-quinolyl dodecyl sulfide required a high temperature. 8-Acetamido-5-amino-6-quinolyl dodecyl sulfide could not be purified, the product oiling from all petroleum ether solvents. This product was acetylated to 5,8-diacetamido-6-quinolyl dodecyl sulfide.

No therapeutic results have been obtained on these compounds.

The ring closure of p-acetoacetanisidide with sulfuric acid to 2-hydroxy-6-methoxylepidine, followed by replacement of the hydroxy group with chlorine using phosphorus oxychloride, was found quite adaptable to large quantities. The reduction of 2-chloro-6-methoxylepidine to 6-methoxylepidine was adapted to the reduction of 200 g. of material, affording a considerable saving in time.

6-Methoxy-4-methyl-2-chloroquinoline was condensed with sodium dodecyl mercaptide in good yield. It was found that if the mercaptan was added to the sodium methyl cellosolve derivative at a low temperature, the condensation could be run without the use of nitrogen.

The recent observation[11] of the favorable physiological action of the 7-chloroquinoline derivatives initiated the preparation of 7-chloro-4-quinolyl dodecyl sulfide, which was obtained from 4,7-dichloroquinoline and sodium dodecyl mercaptide in good yield.

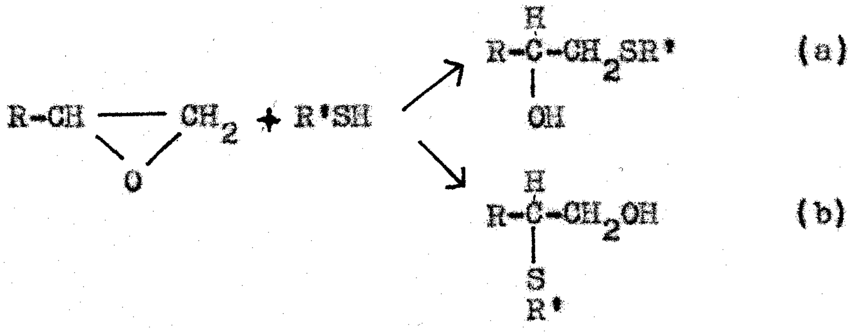
No therapeutic reports have been received on these compounds.

Hydroxy Sulfides

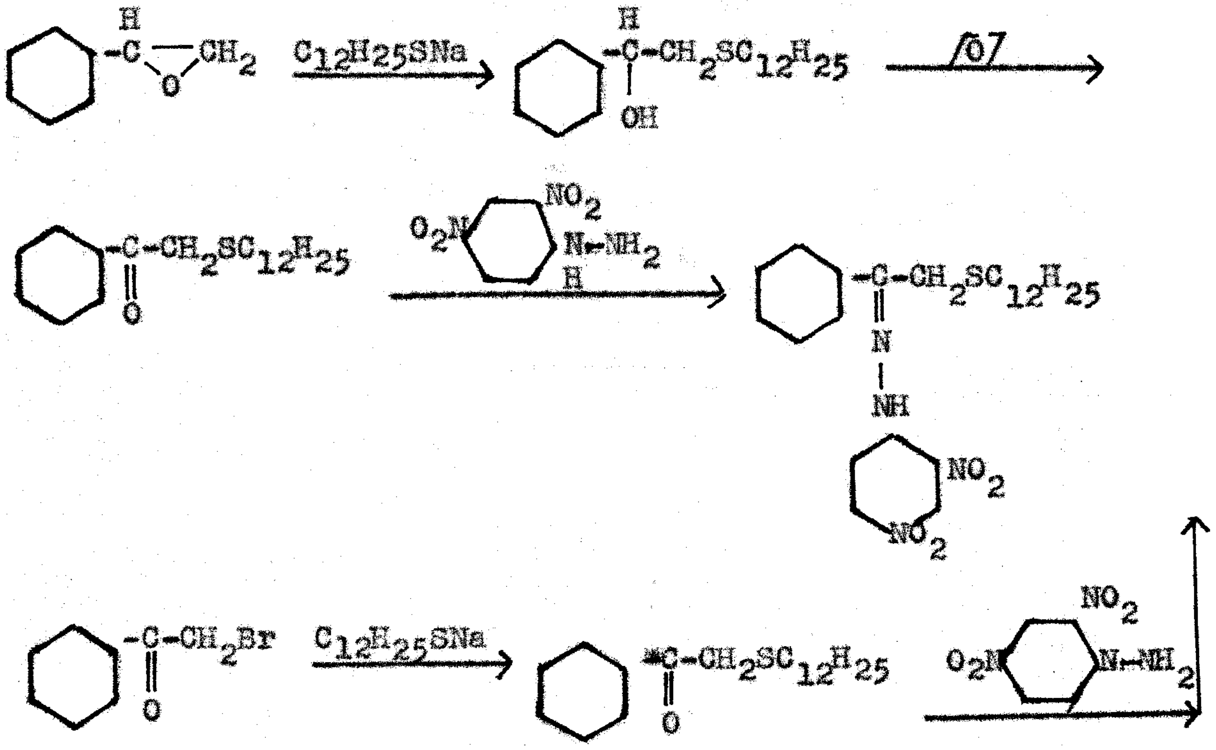
The therapeutic value of the secondary carbinol group and the sulfide group made desirable the combination of these two groups in potential medicinal agents.

1-Diethylamino-2,3-epoxypropane was condensed with sodium dodecyl mercaptide in 58 percent yield. This condensation product could not be oxidized with hydrogen peroxide to either the sulfoxide or the sulfone. 3,4-Epoxybutene-1 and styrene oxide were cleaved in good yield with sodium dodecyl mercaptide and sodium hexadecyl mercaptide.

The reaction of these epoxides with mercaptans can give rise to two products:



It was shown that the cleavage occurred as in method (a) by the following series of reactions:



These results are in agreement with the observations of Fullhart[207] on the cleavage of styrene oxide with sodium methyl mercaptide.

Satisfactory derivatives of 2-phenyl-2-hydroxyethyl dodecyl sulfide could not be prepared. The methiodide proved to be an oil, and the 3,5-dinitrobenzoate melted at 34°. The naphthyl urethan could not be prepared. 2-Hydroxy-3-butenyl dodecyl sulfide would not form an addition compound with gold trichloride nor platinum chloride.

Phenacyl bromide and sodium dodecyl mercaptide reacted in satisfactory yield.

2-Hydroxy-3-butenyl dodecyl sulfide, 2-hydroxy-3-butenyl hexadecyl sulfide, 2-phenyl-2-hydroxyethyl dodecyl sulfide and 2-phenyl-2-hydroxyethyl hexadecyl sulfide were inactive in avian malaria.

Imidosulfides

The CNS group has been shown to be quite effective medicinally.[208] The irritant action of some of the thiocyanates made it desirable, however, to "cloak" this group. It was therefore considered wise to prepare an imidosulfide,  $R-\overset{NH}{C}-SR$, for pharmacological testing.

The saturation by anhydrous hydrogen chloride of a mix-

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207. Fullhart, L., unpublished observation.

208. Arnold, <u>Ber.</u>, <u>75B</u>, 87 (1943).

ture of tetradecyl mercaptan and myristonitrile gave a 65 percent yield of tetradecylimido tetradecyl sulfide hydrochloride. The use of ether as a solvent gave a 55 percent yield. The solubility of this compound in ether undoubtedly accounted for the lower yield.

No report on the physiological activity of this compound has been received.

Thioketones

Freedlander[23b] found that thiobenzophenone had an inhibiting effect against tubercle bacilli. This effect was greater than that of benzophenone, which had been shown to have bacteriostatic action against the bacilli in 1:10,000 dilution.[23a] This suggested the preparation of a long-chained thioketone, such as thiolaurophenone.

The method[209] chosen for this preparation was the preparation of laurophenone dichloride from laurophenone and phosphorus pentachloride, followed by reaction of the dichloride with sodium sulfide.

The reaction of laurophenone with phosphorus pentachloride did not give the expected dichloride, but instead an 88 percent yield of the unsaturated mono-chlorocompound was obtained.

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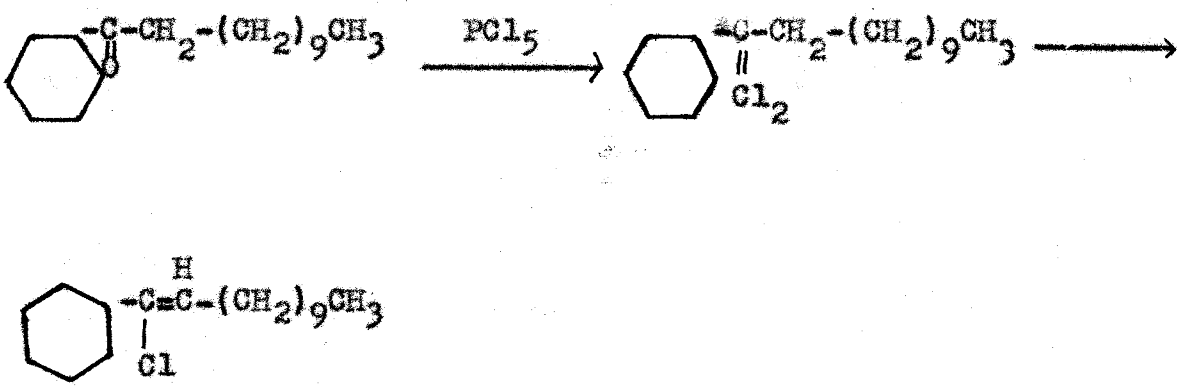
[209] Cf. Staudinger and Freudenberger, Organic Syntheses, Coll. Vol. I, 573 (1944).



The reaction of acetophenone and phosphorus pentachloride has been shown to give 1-phenyl-1-chloroethylene in good yield,[178] but it was hoped that the longer group might stabilize the chain. Apparently the cleavage of hydrogen chloride is immediate and quantitative.

1-Phenyl-1-chlorododecene showed no estrogenic activity at 2 mg. dosage.

No further investigations on the preparation of thiolaurophenone were made.

Mercurials

The germicidal activity of merthiolate suggested the value of changes in its structure. The proposed modification was the preparation of the dodecyl homologue. During these investigations, however, Rumpf[141] in a study of organic mercury compounds and mercapto acids prepared the dodecyl homologue among his other compounds. No report was given of the physiological activity of this compound and so the preparation was continued.

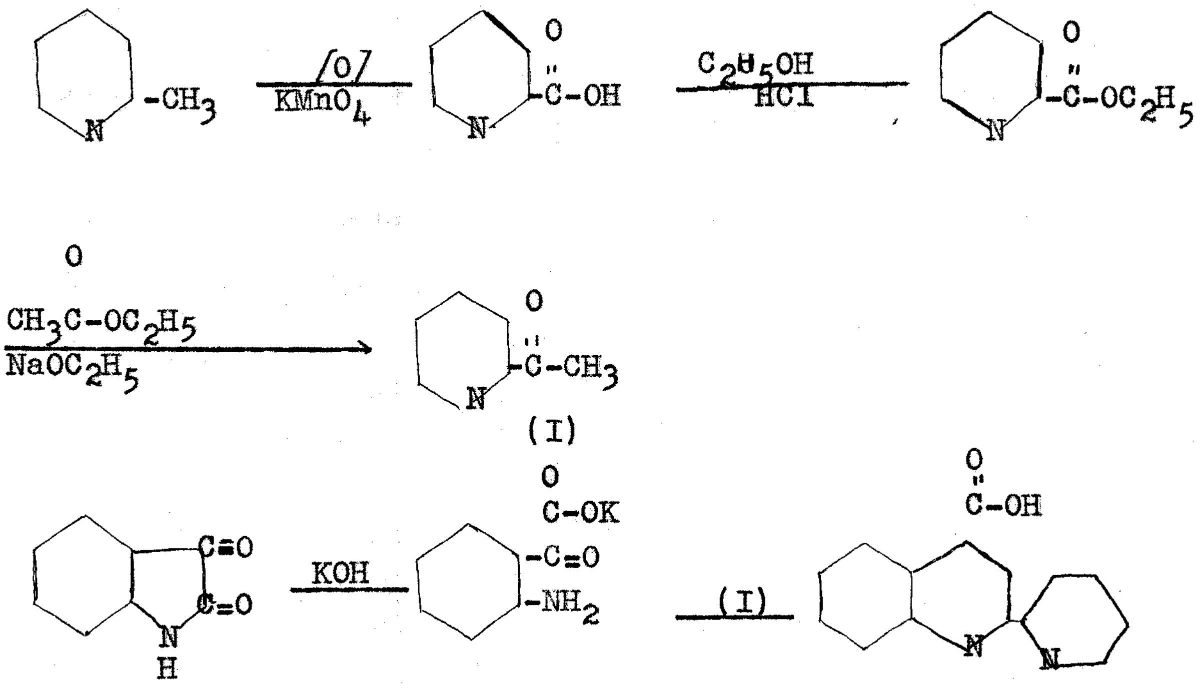
Dodecylmercuric bromide was prepared in 71 percent yield, a 17 percent increase over the yield reported by Meals.[98] Dodecylmercuric bromide and thiosalicylic acid gave *o*-dodecylmercurimercaptobenzoic acid in 15 percent yield. However, the large amounts of recovered dodecylmercuric bromide and dithiosalicylic acid suggest that the thiophenol probably formed the disulfide before the dodecylmercuric bromide could react. Preparation of the thiophenolate under different conditions would probably give a good yield of the product. However, as sufficient product was obtained for testing, the reaction was not further investigated.

D. Miscellaneous Compounds

Cinchononic Acids

The discovery that quinine on oxidation gave 6-methoxycinchoninic acid has stimulated research on these acids. Cinchoninic acids, themselves, have proved to be valuable medicinals, especially in the treatment of gout and rheumatic fever. These therapeutic values in addition to their use as intermediates in the syntheses of antimalarials initiated the preparation of cinchoninic acids.

One of the acids desired was 2-(2'-pyridyl)cinchoninic acid. (XIV). The method chosen for its synthesis was:



Picolinic acid has been prepared by the oxidation of α-picoline with aqueous potassium permanganate,[210] and the method described gave consistent results. The method is described in detail as many directions for the isolation of the acid are incomplete. This method may be of value where a water-soluble acid is prepared. The activity of this compound against the tubercle bacilli *in vitro* was >10.0 (base 2.5).

The use of hydrogen chloride as the esterifying agent in the preparation of ethyl picolinate has been described by Engler[211] and H. Meyer,[212] neither of whom gave a yield. Later workers have not used this method, probably due to the influence of Camps,[213] who pointed out two disadvantages: (1) the clogging of the gas inlet tube, which was successfully avoided in these investigations and (2) the need of a large amount of hydrogen chloride gas. At the same time Camps reported a 90 percent yield using sulfuric acid as the esterifying agent. However, no later workers have reported duplication of his yields. Pinner[214] earlier reported difficulty using sulfuric acid. Neither Wibaut[215] nor Burris and Powell[216] could dupli-

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210. Cf. Singer and McElvain, *Organic Syntheses*, 20, 79 (1940).

211. Engler, *Ber.*, *27*, 1785 (1894).

212. Meyer, H., *Monatsh.*, *23*, 438 (1902).

213. Camps, *Arch. Pharm.*, *240*, 346 (1902).

214. Pinner, *Ber.*, *33*, 1229 (1900).

215. Wibaut, *Rec. trav. chim.*, *45*, 656 (1926).

cate Camps' yield, the former obtaining 49 percent and the latter 30 percent. The use of sulfuric acid probably caused some decarboxylation of the acid as the 2- position in pyridine nuclei is known to decarboxylate easily.

The ester has also been prepared from potassium picolinate and ethyl potassium sulfate with a small amount of ethanol under pressure at 150°.[217]

In these investigations the use of hydrogen chloride as the esterifying agent proved quite satisfactory, the ester being obtained in 73 percent yield with 15 percent recovery of the acid.

Ethyl picolinate had a tuberculostatic activity of 5.0 (base 2.5) and was not clearly analgestic.

Pinner[218] first condensed ethyl picolinate and ethyl acetate using sodium ethoxide as the condensing agent. This condensation has also been carried out in 50 percent yield,[219] using potassium ethoxide and also in 50 percent yield[220] using sodium. Methyl 2-pyridyl ketone has also been prepared in 22 percent yield from 2-cyanopyridine and methylmagnesium iodide,[221] and by the dry distillation of calcium picolinate and calcium

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216. Burris and Powell, J. Am. Chem. Soc., 67, 1469 (1945).

217. Meyer, H., Monatsh, 15, 365 /Beil., Vol. XXII, Springer, Berlin, (1935), p. 35/.

218. Pinner, Ber., 24, 2527 (1891).

219. Clemo, Holmes, and Leitch, J. Chem. Soc., 753 (1938).

220. Winterfield and Holschneider, Arch. Pharm., 273, 315 (1935).

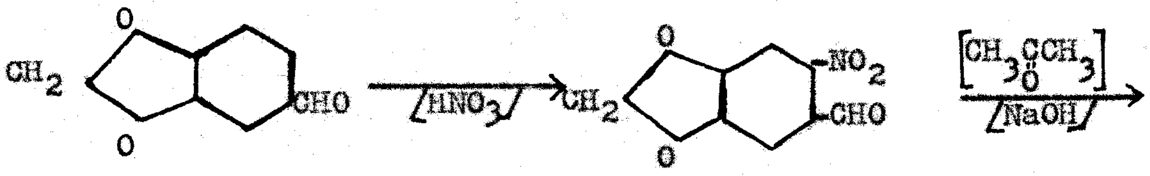
221. Kolloff and Hunter, J. Am. Chem. Soc., 63, 490 (1941).

acetate,[222] no yield being given.

The preparation of methyl 2-pyridyl ketone described in this thesis followed the procedure of Kolloff and Hunter.[221] These workers obtained a yield of 50 percent. By a simple change in the method of working up the reaction mixture yields of 75 percent were consistently obtained. Kolloff and Hunter dissolved their reaction mixture in water and extracted the aqueous solution with ether. These workers then warmed the aqueous alkaline solution to remove the ether. This probably caused basic hydrolysis. In the present investigations when the alkaline mixture was warmed, yields of only 16 and 43 percent were obtained.

2-(2'-Pyridyl)cinchoninic acid was prepared in 81 percent yield from methyl 2-pyridyl ketone and isatin using potassium hydroxide. This product was esterified in 85 percent yield with ethanol by sulfuric acid. Ethyl 2-(2'-pyridyl)-cinchoninate was inactive in tuberculosis [>10 (base 2.5)].

Another product desired was 6,7-methylenedioxy-2-phenylcinchoninic acid (XV). This compound had previously been prepared in poor yield by the following synthesis:[190]



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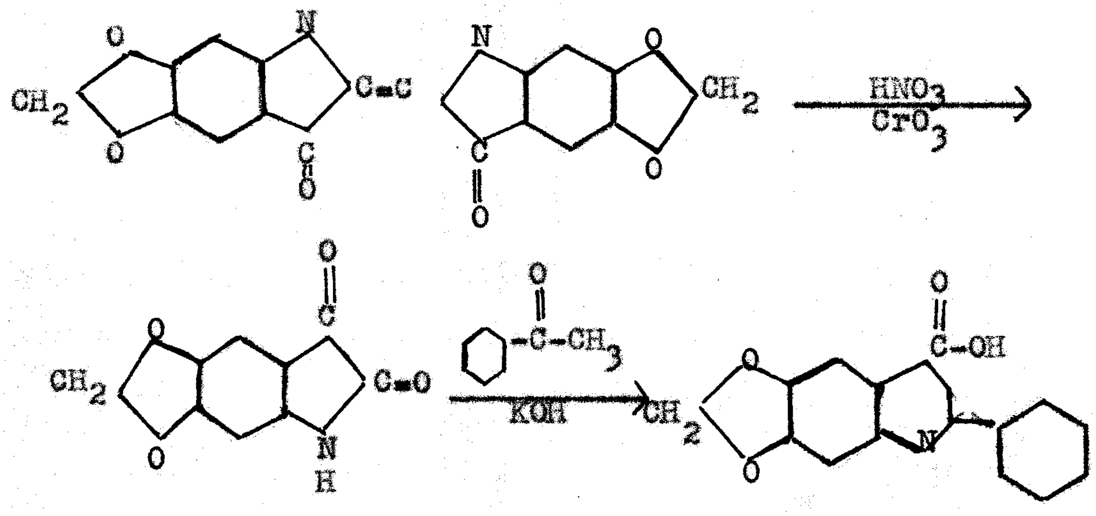
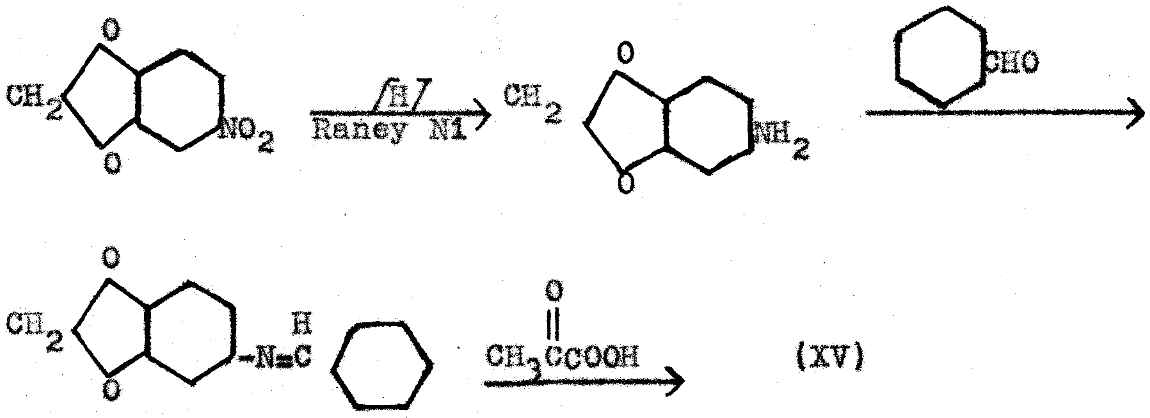
222. Engler and Rosumoff, <u>Ber.</u>, <u>24</u>, 2527 (1891).



(XV)

Attempts to prepare the desired product by this method were not encouraging. No difficulty was experienced in the nitration, but the mixture of nitric and acetic acids was found to give better yields. The condensation to the indigotin derivative in one step was found not so satisfactory as the preparation of the compound in two steps; first, isolation of the addition product obtained when sodium phosphate was used as the condensing agent and second, ring closure using a weakly basic solution. No very satisfactory method of oxidation of the indigotin derivative to 3,4-methylenedioxyisatin was found. The condensation of 3,4-methylenedioxyisatin with acetophenone by potassium hydroxide was fairly satisfactory, considering the purity of the isatin derivative.

These difficulties, however, suggested the desirability of another method and the following synthesis was developed:



(XV)

3,4-Methylenedioxynitrobenzene was obtained in 14 percent yield as a side product in the nitration of piperonal. Reduction using Raney nickel catalyst proved quite satisfactory as did the formation of the anil by the reaction of 3,4-methylenedioxyaniline with benzaldehyde. The condensation of the anil with pyruvic acid went exceptionally well (48%), considering the fact that only one-half of the anil is available. The identity of the acids prepared by the two procedures was proved by the method of mixed melting point of their methyl esters.

Anils

It was recently shown[223] that 6-methoxy-2(3'-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino] quinoline (XVI) was active in experimental avian malarial infections. This com-

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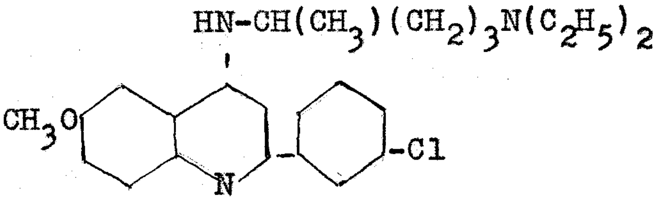
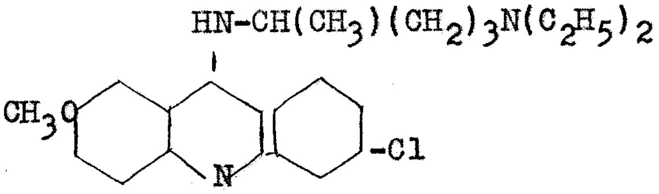
[223] Gilman and Spatz, *J. Am. Chem. Soc.*, *66*, 621 (1944).



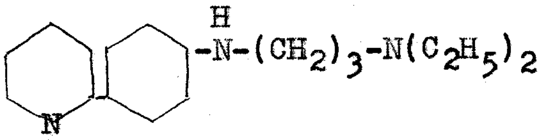
(XVI)

pound, modeled after atebrin (III), had a chlorophenyl group in place of the fuzed chlorobenzo group in atebrin. A related compound, 2-(3'-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutylamino)]-6-methyl quinoline (XVII) was also found active.[224]



(XVII)

Use of the simple central pyridine nucleus of atebrin as a fundamental grouping produced 2-(p-γ-diethylaminopropylaminophenyl)-pyridine (XVIII) which was shown to be active.[225]



(XVIII)

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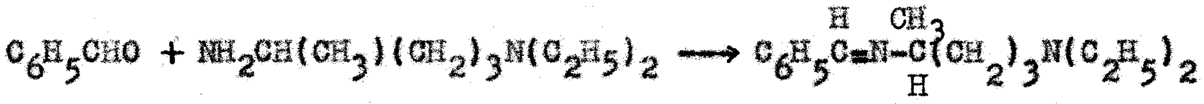
[224] Gilman, Christian, and Spatz, *ibid*, *68*, 000 (1946).

[225] Gilman and Edward, *ibid*, *68*, 000 (1946).

These favorable results indicated that appropriately substituted anils having the azomethine grouping which is present in the above nitrogen heterocycles might be active. Following this idea a series of anils was prepared from 1-diethylamino-4-aminopentane and variously substituted benzaldehydes. The general type of reaction was:



$$C_6H_5CHO + NH_2CH(CH_3)(CH_2)_3N(C_2H_5)_2 \longrightarrow C_6H_5\overset{H}{C}{=}N{-}\underset{H}{\overset{CH_3}{C}}(CH_2)_3N(C_2H_5)_2$$

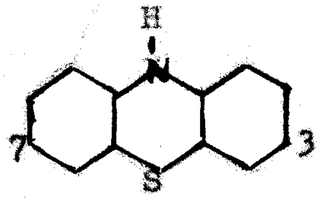
None of these compounds was found active in experimental avian malaria.

Phenothiazine Derivatives

The low toxicity[115] of phenothiazine to animals and its high activity against lower forms of life suggested the introduction of some high-molecular weight aliphatic groups into the phenothiazine nucleus.

It was planned to introduce these groups by means of a Friedel and Crafts reaction. However, since few orientation studies on the phenothiazine nucleus have been made (p. 44), it was desirable to first introduce a lower alkyl group and determine its position.

Phenothiazine was acylated with two moles of acetic anhydride in carbon disulfide to give a diacetyl phenothiazine. The position of the acetyl groups was not determined, but failure of hydrolysis showed that neither group was on the nitrogen atom. This same type of rearrangement has been shown to occur in the carbazole nucleus,[226] and by analogy, the positions of the acetyl group are probably 3 and 7 (XIX):



(XIX)

This work was interrupted, and further investigation was not carried on.

(?),(?)-Diacetylphenothiazine was inactive in tuberculosis /10.0 (base 2.5)/.

Other Miscellaneous Compounds

Dibutylformamide was prepared in 92 percent yield from dibutylamine and formic acid. Its activity on tuberculosis was >10.0 (base 2.5).

A novel method of bromination of allyl groups whereby the gamma carbon atom may be brominated without addition to the unsaturated linkages has been developed by Ziegler[198] and coworkers. This procedure involves refluxing the unsaturated compound with N-bromosuccinimide in carbon tetrachloride.

Ethyl γ-bromocrotonate was desired as an intermediate in another synthesis. This compound has been previously prepared in 60 percent yield by the bromination of ethyl vinylacetate and the removal of hydrogen bromide with sodium ethoxide.[227]

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226. Plant and Tomlinson, J. Chem. Soc., 2188 (1932).

227. Glattfield and Rietz, J. Am. Chem. Soc., 62, 976 (1940).

The dehydration of ethyl 2-hydroxy-3-bromobutyrate with phosphorus pentoxide[228] gave the product in 28 percent yield. It has also been obtained by the reaction of ethyl 2-hydroxycrotonate with phosphorus tribromide in ether[200] (no yield given).

Bromination of ethyl crotonate with bromosuccinimide in carbon tetrachloride afforded 82 percent of ethyl *γ*-bromocrotonate.

3-Diethylamino-2-hydroxybutyronitrile, an intermediate in some antimalarial studies, had been prepared in two steps with an overall yield of 35 percent. In these investigations is described a procedure whereby the two steps were combined and a 62 percent yield was obtained, thus giving considerable improvement in yield and a saving in reaction time.

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228. Braun, *ibid*, *52*, 3173 (1930).

V. SUMMARY

1. General reviews of the chemotherapy of malaria and tuberculosis have been made.
2. A survey of the physiological properties and therapeutic uses of compounds containing high-molecular weight aliphatic groups has been given.
3. The large amount of lipoidal tissue present in certain strains of bacteria, such as the tubercle bacillus, suggested that the introduction into potential physiologically-active structures of groups which would be lipoidal-soluble might give rise to valuable medicinals. This thought initiated the study and preparation of nitrogen and sulfur compounds containing high-molecular weight aliphatic groups as therapeutic agents.
4. Several nitrogen derivatives have been made for therapeutic testing. These agents include dibutylalkylamines and derivatives of tetradecylamine and hexadecylamine.
5. Rearrangement has been shown to occur during the reaction between *α*-halogenonaphthalenes and lithium dialkylamides, *β*-dialkylaminonaphthalenes being formed.
6. Several sulfur derivatives containing high-molecular weight aliphatic groups have been prepared for pharmacological testing. These compounds include quinolyl dodecyl sulfides, hydroxy sulfides, imidosulfides and sulfur-containing mercurials.

7. The reaction between laurophenone and phosphorus pentachloride has been shown to give 1-phenyl-1-chlorododecene-1 in good yield.
8. Several miscellaneous compounds have been prepared for physiological testing. These compounds include anils derived from 1-diethylamino-4-aminopentane, substituted cinchoninic acids and phenothiazine derivatives.
9. Complete pharmacological results are not available, but none of the compounds on which reports have been received has shown any significant therapeutic activity.