1946

Some nitrogen and sulfur containing compounds as chemotherapeutic agents

H. Smith Broadbent
Iowa State College

SOME NITROGEN AND SULFUR CONTAINING COMPOUNDS AS CHEMOTHERAPEUTIC AGENTS

by

H. Smith Broadbent

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.

Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

Iowa State College
1946

ACKNOWLEDGEMENT

The author wishes to express his appreciation to Professor Henry Gilman for his advice, criticism, and encouragement given throughout the course of these investigations.

TABLE OF CONTENTS

I. INTRODUCTION

In the long battle against the biologically debilitating forces of his environment mankind has resorted to many weapons, which may be broadly classified under the headings of surgery, physiotherapy, and chemotherapy. In the broader sense, the chemotherapeutic use of naturally occurring substances has been prevalent since antiquity; however, in the narrower sense of the word, chemotherapy is defined as the use of pure chemical substances or known mixtures of these for medicinal purposes. In the latter sense the use of chemotherapy is relatively modern.

It was not until the remarkable work of Ehrlich in developing salvarsan and its derivatives that the idea of a specificity of different compounds in biological systems was established.

Despite the renewed impetus given to chemotherapy inspired by Ehrlich's prophetic hopes, its advancement lagged except for scattered researches, largely on antimalarials.

Finally the fortunate discovery of the extraordinary therapeutic properties of Prontosil by Domagk and the ensuing development of the "sulfa" drugs again awoke the world to the immense possibilities of chemotherapy.

Since that time research has gone on at a rapidly increasing rate until an immense body of scientific literature

on the subject has been built up. Indeed, there is scarcely a one of man's many ills that cannot be ameliorated today by the use of drugs, many of them unknown before the last decade. Even treatment of the ills of the mind has been distinctly advanced by the use of "shock" therapy employing such drugs as metrazole and by using the opposite effects of the alkaloids of curare.

For many of the protozoan diseases, in fact, there is scarcely any other successful treatment than that of chemotherapy. On the other hand there are a few important diseases on which chemotherapy has had only limited or virtually no success. Much has been done on malaria, but the development of a true prophylactic against all three forms of the disease is still in the future. Tuberculosis and cancer have scarcely been affected at all.

One of the most significant developments in chemotherapy is that of metabolite antagonists,[1] in which a chemotherapeutic agent is pictured as acting in direct antagonism to the synthesis or utilization of an essential metabolite of either an invading microbe or of host cells in such a way as to block their normal mode of action. By this means the effects of the sulfa drugs, arsphenamines, antihistamine, antituberculous, antithyroid, and hemorrhagic agents, and the specificity of the vitamines and hormones have been explained, to mention a

---

1. Roblin, Chem. Rev., 38, 255 (1946).

few examples. Broad applications which bid fair to have the greatest possible importance have been made to the field of immunology.[2]

The mechanism of action of a metabolite antagonist may be to interfere with the essential metabolite by (1) salt or complex formation, (2) chemical reaction, such as oxidation or reduction, forming an inactive product, or by (3) competitively reacting with an enzyme or tissue receptor operating in conjunction with a structurally similar metabolite. The extent to which different chemotherapeutic agents fall under this classification is, of course, largely undetermined. Obviously the last of these mechanisms is the most specific, and also the one heretofore most neglected. To the extent that the mechanism is known by which any particular class of drugs operates, and to the extent that the properties of a new compound can be predicted from a knowledge of those already known, the search for newer and better synthetic chemotherapeutic agents can be guided intelligently. Beyond that point it is largely a matter of chance. The unknown in any field of science is vastly greater than the known. Needless to say, that of chemotherapy is no exception.

It was with the foregoing considerations well in mind that the author embarked on a program of preparing several synthetic compounds which were thought for various reasons

---

2. For a brief sketch of the work and its possibilities see Pauling, Ind. Eng. Chem., News Ed., 24, 1375 (1946).

to have some possibilities as chemotherapeutic agents particularly for the treatment of malaria, tuberculosis, and hyperthyroidism.

During the early part of this work the compounds submitted were put through a standard screening test by the government antimalarial program of the National Defense Research Committee and the Office of Scientific Research and Development to detect possible therapeutic value. The early emphasis in the laboratories at Iowa State College engaged in this work was upon malaria and later shifted to tuberculosis.

Fairly early in the government antimalarial survey program it was noticed that the sulfanilamides had considerable curative action on some forms of avian malaria. The p,p'-diaminodiphenylsulfones, which may be regarded as "rearranged" sulfanilamides, were observed to be even more effective, but also considerably more toxic. Therefore, it seemed of interest to prepare a series of basically substituted diarylsulfides and sulfones for testing as antimalarials. By the time this series was prepared, the intensive investigations by many men associated with the program made it seem likely that no sulfanilamide-type compound was destined to supplant known antimalarials then in use.

By this time, however, the derivatives of p,p'-diaminodiphenylsulfone (Promin, Diasone, etc.) had been found to be

the best chemotherapeutic agents known for the treatment of tuberculosis. Accordingly, the series was submitted for testing as antituberculous agents, and more were synthesized to this end. The results of the tests for which reports have been received are recorded in this thesis.

Of the many thousands of compounds synthesized and tested for antimalarials, those which have shown by far the greater promise, in general, are derivatives of nitrogen-containing heterocycles bearing basic side-chains. Most of such compounds which have been prepared are derivatives of quinoline and acridine. The preparation of relatively very few basically substituted quinoxalines has been reported in the chemical literature, and even fewer have been submitted for testing as antimalarials. Since quinoxaline differs from quinoline only in having a tertiary nitrogen substituted for the carbon in the 4-position of the ring, derivatives of quinoxaline appeared to have some interest as antimalarials. Consequently, a series of these was prepared and submitted for testing.

Within the last three years and especially within the last eighteen months the interest of the medical profession has been greatly attracted toward the use of synthetic drugs in the treatment of hyperthyroidism. Among the types of compounds which seemed destined to be most successful in this regard were the 2-thiouracils. Inasmuch as the thiouracils are nitrogen and sulfur-containing compounds and from the

standpoint of molecular structure serve as more or less of a bridge between the antimalarial and antituberculous agents prepared in these investigations, a series of derivatives of 2-thiouracil have likewise been synthesized and submitted for examination for antithyroid activity.

In resumé, this thesis records the investigations in the synthesis of such nitrogen and sulfur-containing compounds as basically substituted diarylsulfides and diarylsulfones, quinoxalines, 2-thiouracils, and a few miscellaneous compounds for testing as possible chemotherapeutic agents.

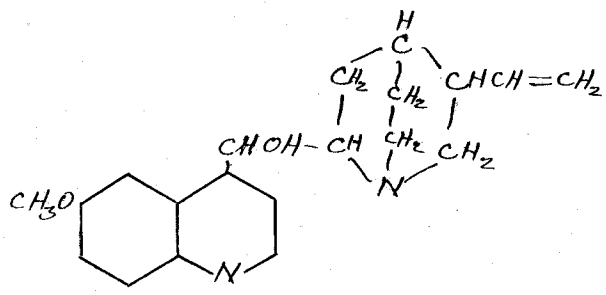
II. HISTORICAL

A. Chemotherapy of Malaria

Since remotest antiquity malaria has probably been man's greatest plague. It is endemic over vast regions of the earth from as far north as Sweden to as far south as the Argentine and Natal, affecting nearly a third of the world's population. It results in over a million deaths per year in India alone and an incomparable economic loss in man hours of work.

Although malaria was first reported by Hippocrates in the fifth century B. C., it was not until 1880 that Laveran discovered the cause of the disease, and somewhat later that Ross established the Anopheline mosquito as the vector.

The earliest successful treatment of malaria (1628) was with the powdered bark of the cinchona tree. The principal active ingredient of this bark is quinine (I).[3]



I

---

3. We owe our knowledge of the structure of quinine largely to Rabe. [See Ber., 41, 62 (1908)]. He climaxed his work

Quinine and its closely related analogs in cinchona have a highly specific action on the schizonts of all three of the recognized forms of malaria in man, benign tertian (P. vivax), quartan (P. malariae), and malignant, subtertian (P. falciparum).[4] Its efficacy increases against them in that order.

Quinine, however, has many drawbacks. It has no prophylactic action; its continued use results in cinchonism and occasionally death, and relapses particularly with benign tertian fever are frequent, to mention a few of them.

An ideal antimalarial should be inexpensive, non-toxic, without cumulative toxicity, administered orally, induce no unpleasant secondary symptoms such as skin discoloration, be effective against all forms of all species of the malarial parasite, and above all be prophylactic.

The search for a synthetic antimalarial possessing these properties to a higher degree than quinine led first to the discovery of the antimalarial action of methylene blue by Ehrlich and Guttmann.[5]

In an intensive campaign carried on by I. G. Farbenin-

---

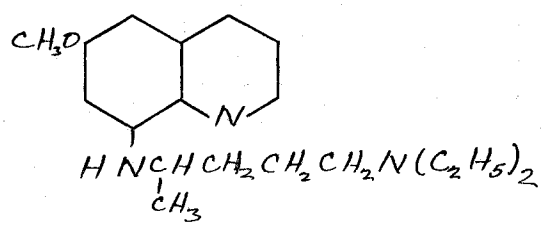
by the total synthesis of hydroquinine, Rabe et al., Ber., 64, 2487 (1931). The total synthesis of quinine itself is due to Woodward and Doering, J. Am. Chem. Soc., 67, 860 (1945).

4. For an excellent treatment of the physiological aspects of malaria see Manson-Bahr, "Manson's Tropical Diseases," William Wood and Co., 1921.

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

dustrie during the first World War and the following decade, some 12,000 compounds were examined, among which were pamaquine (plasmochin) and quinacrine (atebrin). These two synthetic drugs were, until quite recently, the best compounds available for the treatment of malaria.

The first of these to be introduced was pamaquine (II), which is the prototype of most of the more successful variants on quinine available today.[6,7]



II

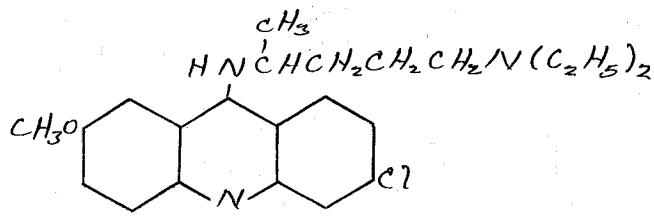
Pamaquine is still one of the most active of all antimalarial drugs, but its toxicity (cyanosis) severely limits its use. It has but slight effect on the schizonts of the malarial parasite; however, it has a powerful effect on the gametocytes, particularly those of P. falciparum. This gametocidal effect, rather uncommon among antimalarials, makes it valuable in preventing transfer of the disease to uninfected mosquitoes.

---

6. Schulemann et al., Ger. Patent 486,079 (1934) [C. A., 24, 1937 (1930)]

7. Roehl, Arch. Schiffs-u. Tropen-Hyg., 30, 311 (1926).

Quinacrine (III) was introduced several years later than pamaquine.[8]



III

It is very similar to quinine in its action on the malarial parasites, but very extensive use during the years of the last war has proved it to be much superior in clinical practice. The principal secondary symptoms accompanying its use are a yellow staining of the skin and gastrointestinal irritation. Notwithstanding the outstanding suppressive action of quinacrine, its lack of gametocidal and prophylactic action leaves much to be desired. Unfortunately, the attempt to couple the schizonticidal activity of quinacrine with the gametocidal activity of pamaquine, is unsuccessful, since the former intensifies the already prohibitive toxicity of the latter.

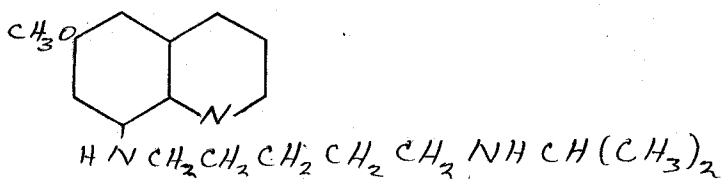
With matters standing at this rather unsatisfactory point at the beginning of World War II, and with the loss of our source of quinine imminent, a broad program was begun

---

8. (a) Mietzsch and Mauss, Klin. Wochschr., 12, 1276 (1933); (b) Ger. Patent 553,072 (1930) [Chem. Zentr., Vol. 103 II, 1201 (1932)]

in this country under the auspices of the National Defense Research Committee for the development of better antimalarials. The thoroughness of this program is attested by the more than 14,000 organic compounds submitted for testing, more than one-half of which were synthesized specifically for the program.[9] A similar program was undertaken in England.

Several new drugs of outstanding properties were prepared and tested. Among the most promising of those having gametocidal activity and a curative action on benign tertian fever, in which respects quinacrine and quinine are lacking, are SN13276 or 6-methoxy-8-(5'-isopropylaminopentylamino)-quinoline (IV)[10] and SN9972, a 5,6-dimethoxy-8-aminoquinoline.



IV

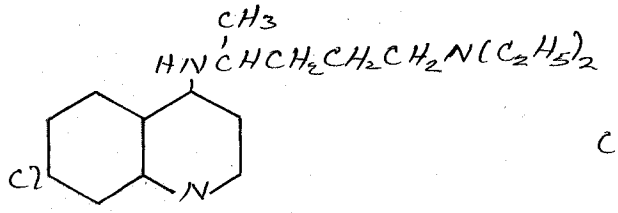
---

9. A complete report of the results of this program comprising a list of the compounds represented by 15,297 Survey Numbers, a history of the pharmacological and clinical studies, summaries of the data obtained from the 100 drugs tested in man, and special survey tables of compounds arranged according to structural relationships is to appear as a monograph on or about November 2, 1946, under the title, "A Survey of Antimalarial Drugs, 1941-1945," F. Y. Wiselogle, Editor. The papers dealing with the syntheses of these drugs are to begin appearing in the July issue of J. Am. Chem. Soc., (1946).

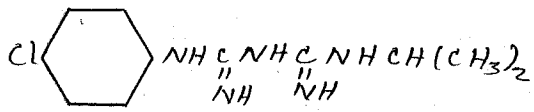
10. Prepared by N. L. Drake and his coworkers at the University of Maryland.

The former cures benign tertian fever at a well tolerated dosage, and the latter is reported to be six times as active as pamaquine and only twice as toxic.[11] Kenneth N. Campbell of Notre Dame has just prepared a 6-methoxy-8-aminolepidine said to have the most extraordinary quinine equivalent of 600 in avian malaria.[11]

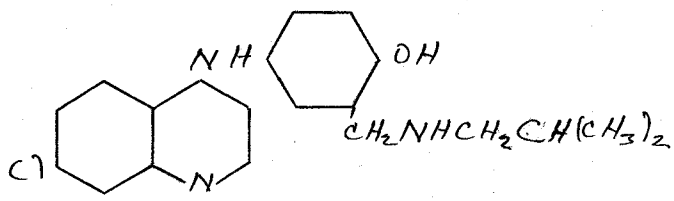
Some of the recently developed, outstanding suppressives are SN7618 or chloroquine, 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline (V), Paludrine, N_1-p-chlorophenyl-N_5-isopropylbiguanide (VI), and the "Mannich base" type, 4-(7-chloro-4-quinolylamino)-α-isobutylamino-o-cresol (VII).



V



VI



VII

---

11. Reported in Chem. Eng. News, 24, 1046 (1946).

Chloroquine (V)[12,13] has much the same mode of action as quinacrine, but it is a distinct improvement on the latter with respect to suppressive action and adverse physiological reactions. As little as one to two days of treatment is reported to cure the *P. falciparum* infections and to terminate clinical vivax infections.[14]

Paludrine (VI) is a development of Imperial Chemical Industries, Ltd. of Great Britain following an exciting series of experiments beginning with pyrimidine derivatives.[15] First clinical reports indicated a phenomenal prophylactic effect as well as a curative action claimed to be better than that of quinacrine or quinine.[16a] Subsequent investigation has somewhat moderated the initial enthusiasm about it; however, it is still an outstanding development. Its chief drawback is an abdominal pain developing on heavy dosage, which is completely removed by the administration of alkali.

---

12. The first reported synthesis was by Anderson, Breitner, and Jung, Ger. Patent, 683,692 (1939) [*C. A.*, 36, 4963 (1942)], who did not recognize its value.

13. Surrey and Hammer, *J. Am. Chem. Soc.*, 68, 113 (1946).

14. (a) Volwiler and MacCorquodale, *Ind. Eng. Chem., News Ed.*, 24, 346 (1946).
    (b) English, Clark, Shepherd, Marson, Krapcho, and Roblin, *J. Am. Chem. Soc.*, 68, 1038 (1946).

15. Curd and Rose, *Chemistry and Industry*, 75 (1946).

16. (a) Curd, Davey, and Rose, *Ann. Trop. Med. Parasitol.*, 39, 208 (1945); Adams *et al.*, *ibid.*, 39, 225, 232 (1945).

The "Mannich base" type (VII) was produced by Burkhalter and his associates of Parke, Davis and Company and announced at the recent Atlantic City meeting (April, 1946) of the American Chemical Society. It has a quinine equivalent of 75 in avian tests and appears to be one of the most encouraging improvements in the 4-aminoquinoline series.

Another recently announced antimalarial is Metachloridine, 2-(m-aminobenzenesulfonylamino)-5-chloropyrimidine for which superiority over quinine and quinacrine as a suppressive agent is claimed.[14] It is reported to have a sulfadiazine equivalent of six and a quinine equivalent of 16 against P. gallinaceum in chicks.

The tremendous number of compounds that have been investigated for antimalarial activity should provide an opportunity unparalleled in the history of chemotherapy for the correlation of chemical structure with activity. The numerous tables of special series to appear in the forthcoming monograph on antimalarial drugs[9] will illustrate many of the relationships that have been found. Good reviews correlating structure with activity for information then available are those of Spatz and of Mosher.[16b,16c]

In reviewing briefly some of the more obvious relation-

---

16. (b) Spatz, S. M., Doctoral Dissertation, Iowa State College, 1941.
(c) Mosher, "Antimalarials: Natural and Synthetic," Confidential Report issued by the research directors of Parke, Davis and Company, Detroit, Michigan, 1942.

ships among the best of all antimalarials so far synthesized, all but paludrine and metachloridine are derivatives of either 6-methoxyquinoline or 7-chloroquinoline or both (as in quinacrine) bearing a basic side-chain on either the 4- or 8- position of quinoline. Metachloridine is a pyrimidine derivative and paludrine may be regarded as derived from pyrimidine as an "open model".[15]

Magidson et al.[17] believe that the basic side-chain confers ability to be absorbed from the gastro-intestinal tract and into the infected erythrocytes upon the molecule of an antimalarial and that the nucleus is the toxophoric or parasiticidal portion of the molecule. Only metachloridine among the drugs mentioned does not have a basic side-chain.

Much less is known about the mechanism of action of the antimalarial drugs than of the sulfa drugs despite the great amount of study expended upon them. It is significant to note that in the aminobenzenesulfonamide series, those which are least inactivated by the administration of p-aminobenzoic acid are the ones most effective in the treatment of malaria.[14b] This would seem to rule out the metabolite antagonist theory, at least as far as PABA is concerned.

Notwithstanding the relatively advanced state of anti-

---

17. Magidson et al., Arch. Pharm. 272, 74 (1934); Ber., 69, 396 (1936).

malarial therapy today, no compound having a truly prophylactic action is known, if indeed one is likely ever to be found, due to the innate limitations of chemotherapy. Furthermore, no entirely satisfactory drug that will completely cure benign tertian malaria, preventing relapses occurring long after it seems to be cured, has yet appeared.

B. Chemotherapy of Tuberculosis

Tuberculosis, the "white plague" of medieval times, has for centuries been one of the most common and most fatal of human diseases, especially in temperate climatic areas. In the more highly civilized countries of the world, both the incidence and severity of the disease has declined greatly in the last one hundred years; nevertheless, tuberculosis is still the most prevalent of all germ diseases with the possible exception of gonorrhea.

Tuberculosis is unique among the common diseases in many respects, and almost all of them contribute to the difficulty in treating it. The causative organism is Mycobacterium tuberculosis, an acid-fast staining organism particularly resistant to destruction by drying or by chemical agents. Unlike the diseases which have yielded most readily to chemotherapy, the protozoan diseases and more recently the streptococcus infections, the tubercle bacilli rarely appear naked

and unprotected in the blood stream. On the contrary, any agent which can hope to affect the tubercle bacilli must overcome the almost unsurmountable hurdle of three distinct barriers.

They are first the avascular bundle of epitheloid cells, the dead and dying members of the reticulo-endothelial system in the area, forming the wall of the tubercle and the caseous center, all the results of the necrotic manifestations of tuberculosis. Then the phagocytic cell, which has engulfed the bacteria but is very frequently unable to destroy them, must often be entered. Finally the tubercle bacillus itself is protected by a relatively impermeable waxy coating.[18]

In view of all this, it is rather remarkable that attempts still persist to treat tuberculosis by chemical means at all. Certainly the dream of Ehrlich, a <u>therapia magna sterilisans</u>, seems exceedingly remote in the case of tuberculosis. As a matter of fact, most authorities fifteen years ago were quite pessimistic due to the conspicuous lack of success always evident when the very numerous chemotherapeutic treatments being prescribed from here and there failed to exhibit the beneficial effects claimed by their sponsors. Writing at about this time Paul Lewis stated, "Certainly it

---

18. For a complete and critical treatment of all the chemical aspects of tuberculosis known at that time the reader is referred to the monumental work of Wells and Long, "The Chemistry of Tuberculosis," Second edition, The Williams and Wilkins Co., Baltimore, Maryland, 1932.

H. C. Wells, L. M. Daniels & E. R. Long.

will be a most unfortunate thing for the progress of tuberculosis research if every substance showing interesting properties in the laboratory is immediately rushed to the clinic regardless of consequences. In this situation patience is to be taken more than usually as an evidence of virtue."[19] We owe most of our early knowledge of the chemotherapy of tuberculosis to the indefatigable labors of Lydia DeWitt and Paul Lewis.

Three different approaches have been made to the chemotherapy of tuberculosis. They have been drugs designed to penetrate the waxy layers surrounding the bacilli, drugs based on the metabolite antagonist approach, and drugs selected or chosen entirely at random, perhaps because of chance beneficial effect on a few cases of tuberculosis. By far the greater number of compounds tested have been in the first and last categories; however, the greatest successes achieved to date have been in the most recently conceived field of metabolite antagonism.

Massie[20] has reviewed the field of tuberculosis chemotherapy particularly with respect to the lipid-soluble agents, in which field he was working. Inasmuch as the researches directed toward the synthesis of possible antituberculous compounds recorded in this thesis were based upon the metabo-

---

19. Quoted by Wells and Long, op. cit., p. 450.

20. Massie, S. P., Doctoral Dissertation, Iowa State College, (1946).

lite antagonist approach, only that phase of the work reported in the literature will be discussed.

In 1940 when scientists everywhere were interested in explaining the remarkable therapeutic activity of the sulfa drugs, Woods and Fildes[21] made the startling announcement that p-aminobenzoic acid (PABA) in relatively small amounts completely vitiated the effects of sulfanilamide *in vivo*. They boldly prognosticated that this indicated that PABA was an essential metabolite of the pathogenic organisms involved and that the structurally similar sulfa drugs acted by being absorbed by the pathogens rather than the essential PABA, thus causing bacteriostasis. The normal body defense mechanisms then were enabled to destroy the microorganisms. The theory has been slow in finding support due to its unorthodox origin; however, Bell and Roblin[22] in a clever investigation were able to thoroughly establish the theory of Woods and Fildes on an experimental basis.

Quite generally there are many antibacterial compounds which inhibit the growth of certain microorganisms requiring a specific growth substance, one might say the microorganisms vitamin, and there exists a more or less definite ratio between the amount of antibacterial present and the amount of the essential metabolite necessary to secure a reversal of

---

21. D.O. Woods and P. Fildes, Chemistry and Industry, 18, 133 (1940).
22. P.H. Bell and R.O. Roblin, J. Am. Chem. Soc., 64, 2905 (1942).

its action.

The theory of metabolite antagonisms has been generalized and extended in recent years until it is probably the most useful concept guiding the chemist in the study of nutritional deficiency diseases, deranged endocrine functions, diseases due to pathogenic organisms, and of immunology.[1]

Obviously a detailed knowledge of the dietary requirements of tubercle bacilli would be invaluable in guiding the synthesis of antituberculous drugs. In its natural environs the tubercle bacilli require a typical diet of nitrogenous material and salts, taking glycerol as its sole source of carbon. Very little about its detailed requirements is known, although it appears to be able to synthesize its own essential metabolites. The bacilli require oxygen, and their growth is inhibited by antioxidants.

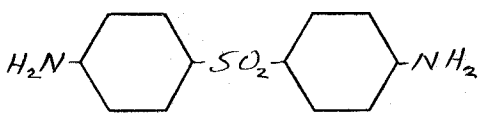
Levaditi and Perault[23] were the first to observe that the antibacterial action of p-aminophenyl sulfones and sulfoxides was reversed by PABA on E. coli and Staph. aureus just as was the action of the sulfonanilamides. On the assumption that the tubercle bacillus, like many other microorganisms requires PABA for growth, a number of investigators[24] testing sulfa

---

23. C. Levaditi and R. Perault, Compt. rend. soc. biol., 139, 1043 (1941).

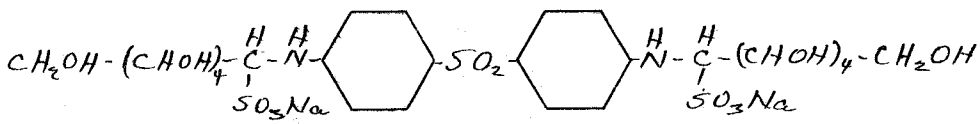
24. The first were Rich and Follis, Bull. Johns Hopkins Hosp., 62, 77 (1938). A good review in this field is that of Corper, Cohn, and Bower, Am. Rev. Tuberc., 40 452 (1939).

drugs on tuberculous guinea pigs observed its inhibitory action. Rist and others[25] soon reported a much stronger inhibiting action in vivo on rabbits using 4,4'-diaminodiphenylsulfone (VIII).



VIII

However, this compound is considerably more toxic, although more potent, than the sulfa drugs. While this work was in progress Feldman, Hinshaw, and Moses[26] were investigating a more soluble and less toxic derivative of 4,4'-diaminodiphenylsulfone which was named Promin, 4,4'-diaminodiphenylsulfone N,N'-bis(glucose sulfonate)(IX).



IX

This drug administered to guinea pigs had a very favor-

---

25. Rist, Bloch, and Hamon, Ann. inst. Pasteur, 64, 203 (1940).

26. Feldman, Hinshaw, and Moses, Proc. Staff Meetings Mayo Clinic, 15, 695 (1940); ibid., 16, 187 (1941); [C. A., 35, 6666, 7534 (1941)].

able effect in halting tuberculosis and promoting healing of the tubercles.

Smith, Emmart, and Westfall[27] in examining the antituberculous activity of seventy-three sulfones, sulfoxides, and sulfonamides obtained good inhibitory action *in vitro* from the following in decreasing order of activity: 4,4'-diaminodiphenylsulfone, 4,4'-diaminodiphenylsulfoxide, sulfathiazole, 4,4'-diaminodiphenylsulfide, sulfadiazine, phosphanilic acid, and promin; however, *in vivo* promin and sulfadiazine were the best.

Callomon and Groskin[28] have reported that Promin is more effective than 4,4'-diaminodiphenylsulfone and the sulfa drugs in guinea pigs.

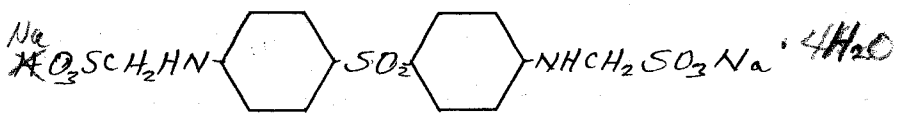
Steenken and Heise[29] found that both promin and its parent sulfone are more active *in vivo* than *in vitro* and also that PABA effectively interferes with their antituberculous activity *in vitro*. They take this evidence to mean that PABA is an essential metabolite of tubercle bacilli.

In applying the known detoxifying effect of sodium formaldehyde sulfoxylate on the arsphenamines to 4,4'-diaminodiphenylsulfone, Raiziss[30] prepared Diasone or 4,4'-diamino-

---

27. Smith, Emmart, and Westfall, *J. Pharmacol.*, 74, 163 (1943).
28. Callomon and Groskin, *Am. Rev. Tuberc.* 47, 97 (1943).
29. Steenken and Heise, *Proc. Soc. Exp. Biol. Med.*, 52, 180 (1943).
30. Raiziss, *Science*, 98, 350 (1943).

diphenylsulfone-bis(N-methylene sodium sulfoxylate) (X).



X

It was found to be decidedly less toxic and even more effective in the treatment of experimental tuberculosis[31,32] than Promin or any other compound tried.

Extensive olinical trials on Diasone and Promin indicate that while they have a favorable effect, the results are somewhat erratic and their toxicity at the necessary dosage levels is a severe drawback. As might be expected they are much more effective on new, rapidly developing lesions approximating the conditions present in guinea pigs where they seemed so promising, than they are in old lesions involving necrosis, caseation, cavitation, and fibrosis.[33]

The newest agent of the amino sulfone type to attract attention is Promizole, 4-aminophenyl-2'-aminothiazoyl-5' sul-

---

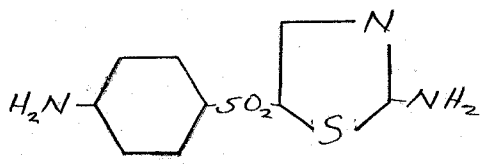
31. Callomon, Am. Rev. Tubero., 52, 1 (1943).

32. Feldman, Hinshaw, and Moses, Arch. Path., 36, 64 (1943).

33. (a) Hinshaw, Pfuetze, and Feldman, Am. Rev. Tuberc., 50, 52 (1944).

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

fone (XI), which was first synthesized by Bambas[34] and later



XI

tested by the Mayo Clinic group. Promizole is of especial interest because it contains the toxophoric p-aminophenylthio group of Promin and Diasone as well as a heterocyclic nucleus, which could readily be the beginning of a new series of active compounds. It is remarkably active in controlling experimental tuberculosis, and more important, it is much less toxic than Promin or Diasone.[35,36] It can be administered safely to humans in doses comparable to those used in the guinea pig; however, it is a potent goitrogenic substance.

The results of clinical experiments are not fully published, but no fully convincing evidence of striking therapeutic effect has been observed.[33b] It does not seem to meet all the critical requirements of a perfect antituberculous compound.

---

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

35. Feldman, Hinshaw, and Mann, Proc. Staff Meetings Mayo Clinic, 19, 25 (1944); Hinshaw, Feldman, and Pfuetze, ibid., 19, 33 (1944); /C. A. 39, 4386 (1945)/.

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

Some extended series of p-aminophenylsulfonyl derivatives have been synthesized for antituberculous activity. Burton and Hoggarth[37,213] report the preparation of a group of substituted aminodiphenylsulfones and sulfonic esters. Only one, 4,4'-diamino-2-hydroxydiphenylsulfone, was comparable in activity to 4,4'-diaminodiphenylsulfone. A series of p-aminobenzenesulfonylalkylcarboxylic acids and their derivatives have been made in the hope of increasing the solubility and decreasing the toxicity of the toxophoric group; however, no therapeutic tests are mentioned.[38]

Bernheim[39] has shown that the oxygen consumption of tubercle bacilli is increased by benzoic and salicylic acids. He, therefore, concludes that they may be essential metabolites. In exploiting this lead Lehmann[40] examined a series of more than fifty substituted benzoic acids for antituberculous activity. The most active of the series was p-aminosalicylic acid (XII), which is strongly bacteriostatic *in vitro*. Clinical trials are underway, but insufficient information to justify conclusions as to its efficacy is available.

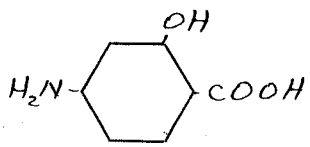
---

37. Burton and Hoggarth, J. Chem. Soc., 468 (1945).

38. Goldberg and Besly, ibid., 566 (1945).

39. Bernheim, Science, 12, 204 (1940); J. Bact., 41, 387 (1941); J. Biol. Chem., 143, 383 (1942).

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



XII

If the 4-amino group is substituted in the 3- or 5- positions or replaced by a nitro-group, the activity disappears; however, N-alkylation does not appreciably affect it. Replacing the hydroxyl group by a methyl group fails to greatly alter the activity of the molecule, but replacement by chloro- or amino- groups destroys its activity. Likewise, substitution into the hydroxyl group or moving it to the 3-position is detrimental. Substitution in the carboxyl group has only slight effect, but its replacement by the sulfonic acid group abolishes activity. If two p-aminosalicylic acid molecules are coupled in the 3-position, an active, but toxic compound results.

Streptothricin and streptomycin have been very promising in the treatment of tuberculosis, but their introduction into therapy is too recent to justify definite conclusions yet, except that they are not without serious drawbacks in clinical use, especially the former.

On the whole, with the possible exception of the mold-produced antibiotics mentioned, the most promising antituberculous drugs examined to date have been the 4-aminophenyl-

sulfone derivatives. While Promin and Diasone have not fulfilled early hopes as remedial agents in tuberculosis, they are now exhibiting highly encouraging results in the treatment of the closely related disease, leprosy.[14a] The most significant point of departure for the synthesis of possible antituberculous drugs still seems to be the p-aminophenylsulfonyl group.

C. Chemotherapy of Hyperthyroidism

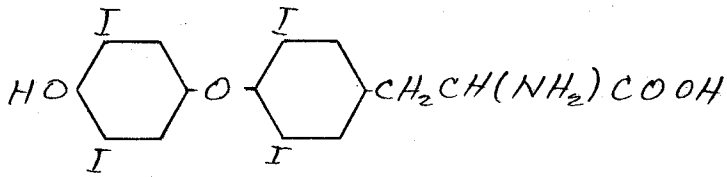
Grave's disease, sometimes called exophthalmic goiter, is characterized by an excessively overactive thyroid gland, the endocrine gland which regulates the rate of metabolism of body tissues by its secretion of the thyroid hormone into the blood stream. It may result in exophthalmos, tachycardia, extreme nervousness, and loss in weight.

The principal treatment of Grave's disease has been surgical removal of a portion of the thyroid after careful observation of the basal metabolic rate of the patient to determine how much to remove. Obviously this is a very delicate operation, for removal of too much of the thyroid may result in hypothyroidism; moreover, the presence of accessory thyroid tissue in the body often makes an accurate estimate of the total amount hazardous.

The thyroid hormone is a colloidal protein, thyroglobulin, secreted by the cuboidal secretory cells lining the follicles

of the vascular gland into the lumen of the follicle under the stimulus of the thyrotropic hormone of the anterior pituitary. The amount of colloid, as it is called, stored in the gland at any time varies widely with different conditions.

The active ingredient of the thyroid hormone is the amino acid, l-thyroxine (XIII), which has only a very slightly lower



XIII

effect on the basal metabolic rate than an equivalent amount of thyroid extract itself.[41,42]

Thyroxine is thought to be synthesized *in vivo* in the following manner:[43,44] iodine concentrated from the body fluids by the thyroid in the form of iodides is first oxidized to iodine, which iodinates tyrosine to form 3,5-diodotyrosine. Two molecules of the latter may then be condensed to give thyroxine by the oxidative removal of the elements of alanine as either serine or as pyruvic acid and ammonia. Another pos-

---

41. For an excellent review of the subject by one of the most outstanding investigators on the subject see Harington, C. R., "The Thyroid Gland, Its Chemistry and Physiology," Oxford University Press, 1933.

42. Salter, W. T., "The Endocrine Function of Iodine," Harvard University Press, 1940.

43. Harington, J. Chem. Soc., 193 (1944).

44. Harington, Proc. Roy. Soc. (London), 132, 223 (1944).

sibility is the direct iodination of a tyrosine-containing polypeptide directly to thyroglobulin.

The functioning of the thyroid gland is controlled by the amount of iodine available to the gland, the process of synthesis of the hormone within the gland, and by its rate of secretion. If for some reason the supply of colloid or secretion runs low, the thyrotropic anterior pituitary hormone increases the activity of the thyroid to make up for this deficit, which is manifest by a hyperplasia or increase in size of the gland. This is readily observed in cases of simple goiter.

Numerous substances have been reported down through the years as having a thyroid inhibiting activity;[45] however, this discussion will include only those appearing to have a specific thyroxine antagonism.

The first to observe such an activity were Mackenzie, Mackenzie, and McCollum[46] in the process of carrying out a nutritional study with sulfaguanidine-fed rats. They noticed that the thyroids of the sacrificed rats showed marked hyperplasia and hyperemia. Histological examination revealed the near absence of the colloid from the glandular tissues. Shortly thereafter a similar phenomenon in phenylthiourea-fed

---

45. Petrova, Advances in Modern Biology (U. S. S. R.), 15, 65, (1942); [C. A., 37, 4139 (1943)].

46. Mackenzie, Mackenzie, and McCollum, Science, 94, 518 (1941).

rats was reported by Richter and Clisby,[47] who suggested that it was due to efforts of the gland to compensate for reduction in the formation of thyroxine, and by Kennedy[48] in establishing allythiourea as the goitrogenic substance in rape seed.

On further investigation the Mackenzies[49] were able to report that a number of the sulfonamides, thiourea, and several of its derivatives had an effect on the thyroid similar to that of sulfaguanidine, reducing the B. M. R. as much as 20 per cent. They further made a number of significant observations on the mode of action of these compounds. Administration of sodium iodide was ineffective in preventing the characteristic symptoms; however, feeding of thyroxine or thyroid extract prevented them entirely. After thyroidectomy these drugs did not further reduce metabolism or eliminate response to thyroxine; moreover, hypophysectomy eliminated the thyroid alterations caused by them. They concluded from these data that the drugs acted primarily by interfering with the normal synthesis of the thyroid hormone by the gland, and that hyperplasia was the result of the compensatory action of the pituitary.

They listed a number of inactive substances as well. Notable among the group were the aryl amines in which the

---

47. Richter and Clisby, Proc. Soc. Exp. Biol. Med., 48, 684 (1941); Arch. Pharm., 33, 46 (1942).

48. Kennedy, Nature, 150, 233 (1942).

49. Mackenzie and Mackenzie, Federation Proc., I, 122 (1942); Endocrinology, 32, 185 (1943).

amino group was substituted such as urea, phenylurea, cystine, thiamine, and sulfanilic acid.

Meanwhile Astwood et al.[50] had independently arrived at the same conclusions. They gave a rough quantitative evaluation of the "sulfa" drugs. They observed that not only was thyroid hyperplasia prevented by thyroid powder, but that these drugs had no effect on the toxic or calorigenic activity of thyroid powder in normal or hypophysectomized rats.

The possibilities of treatment of hyperthyroidism in man[51,52,53] became responsible for a great deal of interest in thyroxine antagonists. Hereafter frequent reports appeared of investigations of various compounds for antithyroid activity.[54] Only what are deemed to be the most significant findings will be recounted herein.

Astwood[55] presented the first extensive study listing the antithyroid properties of one hundred and six compounds. The active ones were divided into two classes, those con-

---

50. Astwood, Sullivan, Bissell, and Tyslowitz, Endocrinology, 32, 210 (1943).

51. Astwood, J. Am. Med. Assoc., 122, 78 (1943).

52. Himsworth, Lancet, 1943 II, 465.

53. Williams and Bissel, Science, 98, 156 (1943).

54. For a review more complete in this respect than the present one see reference 1.

55. Astwood, J. Pharmacol., 78, 79 (1943).

taining the thioureylene grouping (-NHC(=S)NH-) and certain aniline derivatives, the former class being more active than the latter. In the former class he found 2-thiouracil, 2-thiobarbital (he mistakenly referred to it as 2-thiobarbituric acid, but later rectified his error),[56] N,N-diethylthiourea, and 5-benzal-2-thiohydantoin more active than thiourea in that order, and aryl and alkyl derivatives of thiourea less active with the above-mentioned exception. The 2-thiohydantoins proved to be excessively toxic. The effective aniline derivatives were the sulfonamides, o-,m-,-p-aminobenzoic acids, p-aminophenylacetic acid and its anilide. The inactive compounds contained certain modifications of the above groupings which were such as to lead him to conclude that the above-mentioned groups were essential to activity; however, inclusion of the thioureylene grouping intact in a five or six membered ring enhanced activity.

He suggested that the active aniline derivatives probably acted through a competitive mechanism with the enzyme system oxidising diiodotyrosine to thyroxine whereas the thiourea derivatives might act as possible specific inhibitors of the system. These results were reported in only a rough quantitative manner. A reliable quantitative method of evaluating antithyroid drugs was later worked out by Astwood et al.,[57]

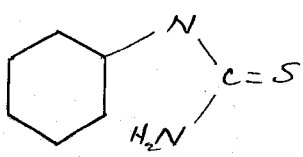
---

56. Astwood, Bissell, and Hughes, Endocrinology, 36, 72 (1945).

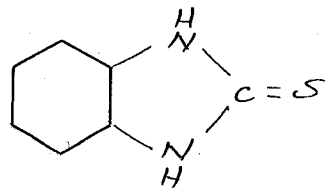
57. Astwood and Bissell, Endocrinology, 34, 282 (1944).

which they subsequently used, arbitrarily choosing the activity of thiouracil as 1.0.

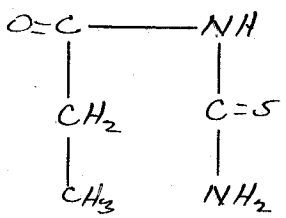
McGinty and Bywater[58] then published a report of the testing of fifty-six varied compounds in which they used virtually the same criteria as Astwood,[57] but chose to rate thiouracil as 100 rather than as 1.0. This appears to be a fortunate choice since thiouracil is one of the most active of all compounds investigated. Where duplications occurred they agreed well with Astwood. Aside from uncovering three new rather active compounds, pyridine-2-thiol (23), thiazoline-2-thiol (131) and benzimidazole-2-thiol (116), their principal contribution to the correlation of activity with structure was the observation that ring compounds were markedly more effective than the corresponding open-chain analogs.



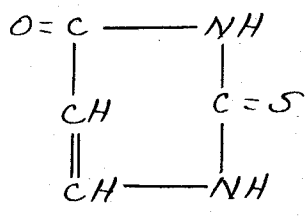
Phenylthiourea (14)



Benzimidazole-2-thiol (116)



Propionylthiourea (14)



2-Thiouracil (100)

---

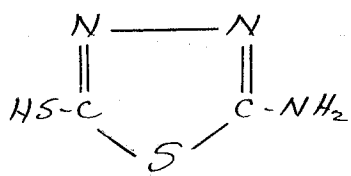
58. McGinty and Bywater, J. Pharmacol., 84, 342 (1945).

To be strictly analogous the latter should refer to dihydrothiouracil, which is only one-tenth as active.

They suggested that this interesting comparison might be due to the much greater tendency for the ring compounds to exist in the tautomeric thiol form, a surmise which has been well supported by later work, incidentally.

In a study of twenty-six derivatives of benzimidazole-2-thiol and imidazoline-2-thiol, Bywater et al.[59] found them all to be less active than the parent compound itself. Substitution with halogen, alkoxyl, or alkyl groups reduced activity. Altering the thioureylene grouping virtually destroyed all activity. Nevertheless, the closed-chain hypothesis received additional support.

In still another study these workers[60] examined a series of thirty-eight sulfones and sulfur-containing heterocycles. In general they were unpromising. Promizole showed some activity (18). Interestingly, "Promizole sulfide" showed even greater effect (53); this was a general trend. The most active compound uncovered was 5-aminothiadiazole-2-thiol (XIV).



XIV (156)

---

59. Bywater, McGinty, and Jenesel, J. Pharmacol., 85, 14 (1945).

60. McGinty and Bywater, J. Pharmacol., 85, 129 (1945).

Its close relationship to other active compounds is obvious. Substitution for the thiol hydrogen greatly reduces its effectiveness.

Meanwhile a study conducted by Astwood *et al.*[61,62] on over two hundred additional compounds using their improved assay, rating thiouracil as 1.0, gave some interesting results. They corroborate the findings of McGinty and Bywater[58] on some of their most active compounds, viz., imidazole-2-thiol and 5-amino-1,3,4-thiadiazole-2-thiol. They suggested that the presence of the thioureylene grouping alone was insufficient to confer activity upon a compound. For example, only the 2-thiobarbituric acids di-substituted in the 5- position were active. The 5,5-diethyl derivative, thiobarbital (1.7), was the most potent member of this series, the dimethyl derivative being only one-tenth as active. While isothioureas were of no value, incorporation of the sulfur into the ring as in 2-amino-thiazole did not abolish activity (0.1). Tetra-alkylation of thiourea increased its activity as much as three-fold, in the case of tetramethylthiourea, in spite of the fact that tautomerization to the supposedly essential thiol form is then prevented; however, both compounds react readily with iodine.[63]

---

61. Astwood, "Harvey Lectures," Science Press Printing Co., Lancaster, Penn., 1945.

62. Astwood, Bissell, and Hughes, Endocrinology, in press.

63. Miller, Roblin, and Astwood, J. Am. Chem. Soc., 67, 2201 (1945).

The most effective series thus far tested was among those reported. This was a series of 5-and/or 6-alkyl or aryl substituted 2-thiouracils synthesized by Anderson et al.,[64] and later tested in man.[65] The most active members were 6-n-propyl-2-thiouracil, 6-ethyl-2-thiouracil, and 6-benzyl-2-thiouracil having activities of 11.0, 8.0, and 10.0, respectively; thus they are at least six to seven times as effective as any other compound heretofore reported. Introduction of polar groups such as amino, cyano, carbethoxy, and chloro groups, either directly into the hetrocyclic ring or on a substituent phenyl group, almost completely destroyed activity.

Williams and Frame[66] have published a report that non-thiourea sulfur compounds, isothioureas, and thioureas wherein the sulfur atom is included in a ring are inactive.

In clinical studies Astwood,[51] who made the first of these, reported that patients suffering from hyperthyroidism returned to normal in one to two weeks; however, they usually reverted back when treatment stopped. 2-Thiouracil seems to be of definite value in preoperative treatment of severe hyperthyroidism. A number of reports of severe toxic reactions have been published.

---

64. Anderson, Halverstadt, Miller, and Roblin, ibid., 67, 2197 (1945).

65. Astwood and VanderLaan, J. Clin. Endocrinol., 5, 434 (1945).

66. Williams and Frame, Bull. Johns Hopkins Hosp., 77, 314 (1945).

Cookson[67] has reported favorably on the effect of 2-thiouracil administered to patients with hyperthyroid. It does not appear to reduce exophthalmos however. Thiobarbital is reported to be about twelve times as effective in man as 2-thiouracil, but its use results in an even higher percentage of toxic manifestations than the latter.[68] Of all compounds clinically tested, 6-n-propyl-2-thiouracil seems to be the most satisfactory.[65] It is at least five times as active as 2-thiouracil in man; its effect is more lasting, and its toxic manifestations are very much less.

It is evident that the chemotherapeutic approach to the treatment of hyperthyroidism is still in its infancy. Such drugs as 2-thiouracil effect permanent cures only in mild cases. A drug which will actually rectify the malfunctioning of the thyroid by restoring its regulatory system to normal operation is the most satisfactory answer.

A precise explanation of the mechanism by which the normal thyroid acts is a necessary adjunct to a fuller understanding of the mechanism governing the action of antithyroid drugs. This further handicaps intelligent search for newer and better drugs. Specific inhibition of the thyroid enzyme system responsible for oxidising iodide to iodine is the most favored explanation for the action of antithyroid drugs.[61]

---

67. Cookson, Lancet, 249, 485 (1945).

68. Bartels, J. Am. Med. Assoc. 129, 932 (1945).

This would require a system of rather high potential such as a peroxidase and hydrogen peroxide. Histochemical evidence for a peroxidase in thyroid tissue has been presented,[69] but another could not isolate one by chemical means and casts doubt upon the report.[70] By the use of redox indicators the potential of the normal thyroid cell was shown to be over +.050 volt and that of the colloid -0.20 volt. Both assumed the higher value when activated and were reduced to the lower value by thiourea.[71] Envolvement of the cytochrome-cytochrome oxidase system seems to be ruled out since thiouracil among other compounds has no effect on the oxygen consumption of surviving thyroid tissue slices.[72]

Many investigations using radioactive iodide, NaI^{131}, on surviving thyroid tissue slices have been carried out.[73,74,75,76] While there is some dispute as to whether the

---

69. Dempsey, Endocrinology, 34, 27 (1944).

70. Glock, Nature, 154, 460 (1944).

71. De Robertis and Goncalvis, Endocrinology, 36, 345 (1945).

72. Lerner and Chaikoff, Endocrinology, 37, 363 (1945).

73. Franklin, Lerner, and Chaikoff, J. Biol. Chem., 153, 151 (1944); Endocrinology, 34, 265 (1944).

74. Franklin and Chaikoff, J. Biol. Chem., 148, 719 (1943); ibid., 152, 295 (1944).

75. Keston, Goldsmith, Gordon, and Charipper, ibid., 152 241 (1944).

76. Rawson, Tannheimer, and Peacock, Endocrinology, 34, 345 (1944).

iodine gathering ability of the thyroid is decreased by antithyroid drugs, there seems to be no question that the conversion of iodide to diiodotyrosine and thyroxine is interfered with. The need for caution in evaluating such work has been emphasized by the report that a rapid interchange of radioactive iodine for ordinary iodine may readily take place in organic compounds under some conditions.[77]

It has been suggested that the antithyroid effects of thiourea are related to its ease of reaction with iodine.[78] In applying this suggestion to 2-thiouracil and other active compounds, Astwood *et al.*[63] found that in neutral buffered solutions, the drugs reacted with several equivalents of iodine so rapidly that casein and tyrosine could not be iodinated in their presence.

On the basis of the evidence so far accumulated one may conclude that the substituted 2-thiouracils have greater promise as antithyroid drugs than other types and that efforts directed toward the synthesis of new members of this series will be profitable.

---

77. Miller, Anderson, Madison, and Salley, Science, 100, 340, (1944).

78. Campbell, Landgrebe, and Morgan, Lancet, 1944, II, 630.

TABLE I

Some Active Antithyroid and Related Compounds[79]

Name of Compound	Activity[80]
Sulfanilamide	+++
Sulfaguanidine	++++
Sulfanilylurea	+
Sulfadiazine	++++
Thiourea	9
Ethylthiourea	35
N,N'-Diethylthiourea	47
N,N'-Di-n-butylthiourea	9
Phenylthiourea	14
Tetramethylthiourea	30
4,4'-Diaminodiphenylsulfide	15
4,4'-Diaminodiphenylsulfone	4
4-Aminophenyl-2'-amino-5'-thiazoyl sulfide	53

79. This table is designed to show a representative cross section of the active compounds investigated and to illustrate some of the more evident correlations of activity with structure.

80. Where quantitative data are available, the activities of these compounds have been computed to a common basis, viz. 2-thiouracil equals 100. Otherwise activity is merely designated by plus signs in a rough quantitative manner.

TABLE I (Continued)

Name of Compound	Activity
4-Aminophenyl-2'-amino-5'-thiazoyl sulfone	18
Naphthalene-2-thiol	0
Pyridine-2-thiol	33
Thiazoline-2-thiol	131
Benzimidazole-2-thiol	116
Imidazoline-2-thiol	63
1-Methylbenzimidazole-2-thiol	3
Benzimidazole	tr.
5-Amino-1,3,4-thiadiazole-2-thiol	156
2-Aminothiazole	10
5-Benzal-2-thiohydantoin	++
2-Thiobarbituric acid	0
5,5-Diethyl-2-thiobarbituric acid	123
5-Ethyl-5-isoamyl-2-thiobarbituric acid	5
2-Thiouracil	100
6-Methyl-2-thiouracil	104
5-Ethyl-2-thiouracil	350
6-Ethyl-2-thiouracil	800
5,6-Diethyl-2-thiouracil	200
6-n-Propyl-2-thiouracil	1100
6-Isopropyl-2-thiouracil	900

TABLE I (Continued)

Name of Compound	Activity
6-Phenyl-2-thiouracil	100
6-Benzyl-2-thiouracil	1000
6-p-Chlorophenyl-2-thiouracil	0
6-Amino-2-thiouracil	0
5-Cyano-2-thiouracil	0
p-Aminobenzoic acid	0.3
4,4'-Diaminobenzil	15

D. Methods of Preparation

Aminodiaryl Sulfides

A considerable number of methods have been used for the preparation of aminodiaryl sulfides employing, in the broad sense, two different approaches as follows: condensation of compounds containing amino or substituted amino groups to form the diphenyl sulfide nucleus, and condensation of compounds containing precursor groups, usually nitro or halo, which can later be converted to amino groups, to form the desired nucleus.

Direct substitution into diphenyl sulfide is very rarely used as a means for preparing its derivatives.

The most generally useful approach to the aminodiphenyl sulfides is the condensation of a suitably substituted mercaptide with an activated aryl halide.[81,82] The most common activating group is the nitro group, which can later be reduced by stannous chloride,[81] tin and hydrochloric acid, iron and water,[83] or other chemical means. Aryl halides which lack activating groups will not undergo metathesis.

If p-nitrochlorobenzene is heated with sodium sulfide, the aryl groups are condensed to the sulfide, and one of the nitro groups is simultaneously reduced to give 4-nitro-4-aminodiphenyl sulfide.[84,85] p-Bromonitrobenzene heated with sulfur and alcoholic alkali is reported to yield 4,4'-dinitrodiphenyl sulfide among other things.[86] Arylsulfinic acids heated with aniline give p-aminodiphenyl sulfides as the principal products.[87] Thioaniline, 4,4'-diaminodiphenyl

---

81. Bourgeois and Huber, Rec. trav. chim., 31, 30, 38 (1912).

82. Bost, Turner, and Norton, J. Am. Chem. Soc., 54, 1985 (1932).

83. Cullinane and Davies, Rec. trav. chim., 55, 885 (1936).

84. Gabel and Grinberg, J. Applied Chem. (U. S. S. R.), 12, 1484 (1939); Gabel and Shpanion, ibid., 12, 1489 (1939).

85. Raiziss, Clemence, Severac, and Moetsch, J. Am. Chem. Soc., 61, 2763 (1939).

86. Fromm and Wittmann, Ber., 41, 2264 (1908).

87. Hinsberg, Ber., 36, 114 (1903); Heiduschka and Lamdkammer, J. prakt. Chem., [2] 88, 439 (1913).

sulfide, may also be made merely by heating sulfur and aniline together at 160°.[88] Unsymmetrical diaryl sulfides can be prepared by the reaction of diazonium salts with sodium mercaptides and decomposing the intermediate diazosulfides by warming.[89,90] Arylsulfenyl halides will condense with phenols or arylamines in the o- or p- positions with the elimination of a hydrogen halide forming the corresponding diaryl sulfide.[37]

The aminodiaryl sulfides are rather weak bases, only slightly soluble in aqueous acids; hence difficulty is often experienced in carrying out reactions involving diazonium intermediates such as deaminations,[91] hydrolyses,[81] and Sandmeyer reactions.[92] A generally useful method of diazotization in such cases would seem to be that of Hodgson and Walker[93] involving the addition of a solution of the amine in glacial acetic acid solution to one of sodium nitrite in concentrated sulfuric acid.

A unique series of aminodiphenyl sulfides has been reported substituted in the amino group by the condensation of

---

88. Hinsberg, Ber., 38, 1131, 1134 (1905).

89. Ziegler, Ber., 23, 2471 (1890).

90. Hilbert and Johnson, J. Am. Chem. Soc., 51, 1526 (1929).

91. Kehrmann and Bauer, Ber., 29, 2464 (1896).

92. Ganapathi and Venkataraman, Proc. Indian Acad. Sci., 21A, 34 (1945).

93. Hodgson and Walker, J. Chem. Soc., 1620 (1933).

the aminodiphenyl sulfide with formaldehyde and a heterocycle carrying an active hydrogen atom. For example, 4-nitro-4'-aminodiphenyl sulfide condensed with α-picoline in the presence of paraformaldehyde gives 4-nitro-4'-{[2-(pyridyl) ethyl]amino}diphenyl sulfide.[92]

Aminodiaryl Sulfones

Aminodiaryl sulfones can probably best be prepared, in general, by oxidation of suitably substituted acetylamino or nitrodiaryl sulfides to the corresponding sulfones followed by hydrolysis or reduction to the desired compounds. Aminodiphenyl sulfides cannot be directly oxidised to the sulfones because of the destructive effect of the oxidising agent. A number of oxidising agents have been employed: potassium permanganate,[81] potassium dichromate,[85] chromic acid,[94,95] and hydrogen peroxide,[82,96,97] being the most frequently used. By far the best of these is hydrogen peroxide (30% aqueous solution). It is not only cleaner, more rapid and convenient, but it is more selective in its action. Alkyl side-chains are not oxidised as may easily occur with the other oxidising

---

94. Shriner, Struck, and Jorison, J. Am. Chem. Soc., 52, 2060 (1930).

95. Buehler and Masters, J. Org. Chem., 4, 262 (1939).

96. Hinsberg, Ber., 43, 289 (1910); Pummerer, Ber., 43, 1407 (1910).

97. Van Arendonk and Kleiderer, J. Am. Chem. Soc., 62, 3521 (1940).

agents named. Acetone or acetic acid are usually employed as solvents.

The other general approaches to the synthesis of aminodiaryl sulfones are condensations of appropriately substituted compounds to give the amino compounds directly or their acylated derivatives and those condensations whose primary products are sulfones from which the amino compounds are derived by reduction or substitution.

A number of applications of the Friedel-Crafts or related reactions have been employed. From p-acetaminobenzenesulfonyl chloride and acetanilide in the presence of anhydrous aluminum chloride the formation of 4,4'-diacetylaminodiphenyl sulfone is claimed.[98] One or both components must have an amino or acetylamino group to facilitate the reaction. While acetanilide is merely chlorinated by sulfuryl chloride in the presence of aluminum chloride, by the use of thionyl chloride in carbon disulfide solution (tetrachloroethane is unsuitable), 4,4'-diacetylaminodiphenyl sulfoxide is obtained, which can readily be oxidised to the corresponding sulfone.[99] When various halo-, alkyl-, or nitrobenzenesulfonyl chlorides are heated at high temperatures with aromatic hydrocarbons or their oxides in the presence of ferric chloride, the corresponding

---

98. Kereszty and Wolf, Hung. Pat., 130,021 /C. A., 33, 4600 (1939).

99. Sugasawa and Sakurai, J. Pharm. Soc. Japan, 60, 33 (1940).

sulfones are said to be formed.[100] Loudon and Robson[101] were able to smoothly condense 4-chloro-3-nitrobenzenesulfonyl chloride with chlorobenzene in the presence of aluminum chloride to form 4,4'-dichloro-3-nitrodiphenyl sulfone.

4,4'-Diaminodiphenyl sulfone has been prepared by the amination of 4,4'-dichlorodiphenyl sulfone with 28% aqueous ammonia at 200°C. using cuprous bromide and copper bronze catalyst.[102] The chloro sulfone may be prepared by treating chlorobenzene with sulfuric acid at high temperature.[103]

The product appears to be formed by the action of sulfur trioxide and not by condensation of the intermediately formed sulfonic acid with the hydrocarbon.

The most generally useful condensation method for making diaryl sulfones is the condensation of the salts of arylsulfinic acids with activated halobenzenes in various high boiling solvents.[101,104,105] The sulfinates are not quite so active in methathesis as the mercaptides; therefore, the method of choice may be to take the alternate route employing

---

100. Huismann, Ger. Patent, 701,954 /C. A., 36, 98 (1942)/.

101. Loudon and Robson, J. Chem. Soc., 242 (1937).

102. Heymann and Fieser, J. Am. Chem. Soc., 67, 1979 (1945).

103. Meyer, Ann., 433, 339 (1923).

104. Loudon, J. Chem. Soc., 220 (1936).

105. Roblin, Williams, and Anderson, J. Am. Chem. Soc., 63, 1930 (1941).

mercaptides, and then, to oxidise the sulfides obtained to the sulfones.

Amino sulfones have been prepared by the action of sulfinic acids on phenylhydroxylamine, which yields the 4-amino compound,[106] and by the action of arylsulfonic acids on arylamine hydrochlorides in the presence of phosphorus pentoxide.[106]

Sulfinic acids, like the mercaptides, react with diazonium salts forming diazosulfones which decompose to sulfones on heating; however, the reaction seems to have found little use as a means of synthesizing aminoaryl sulfones because of rearrangements which occur as the diazosulfone decomposes.[107]

The ease with which sulfinic acids undergo 1,4-addition to quinones has been utilized in preparing aminodiphenyl sulfones.[37]

Injectable solutions of 4,4'-diaminodiphenyl sulfone have been prepared by introducing such water-solubilizing groups as the carboxyacylamido groups into the molecule. For instance, 4,4'-diaminodiphenyl sulfone on treatment with ethyl oxalate and subsequently hydrolyzed, yields 4,4'-bis(carboxyformamido) diphenyl sulfone, and treatment with malonyl chloride gives the corresponding acetamido derivative.[108]

---

106. Bamberger and Rising, Ber., 34, 244 (1901).

107. Hantzsch, Ber., 31, 636 (1898).

108. Gray and Platt, J. Chem. Soc., 42 (1942).

Chardonnens and Ventz[109] report a rather unique property of 4-methyl-3-nitrodiphenyl sulfone. In the presence of piperidine it condenses with benzaldehyde to give 4-styryl-3-nitrodiphenyl sulfone and with p-dimethylaminonitrosobenzene to give the corresponding anil, which is readily cleaved with hydrochloric acid to 4-formyl-3-nitrodiphenyl sulfone. 3-Methyl-5-nitrodiphenyl sulfone behaves in a similar manner.

In synthesizing the more complex nitrodiaryl sulfones, the complex replacement reactions made possible by the preeminent capacity of the nitro and phenylsulfonyl groups to activate their respective o,p-positions should be noted. The mobility of groups in the dinitrochlorobenzenes is similarly conditioned, but much less complex. Loudon and his collaborators[101,104,110] have published a series of investigations of this phenomenon dealing with its theoretical consequences.

Quinoxalines

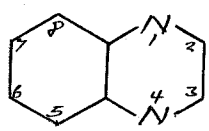
The methods of preparing quinoxalines may be classified into two categories. Two or more compounds bearing the desired substituents are condensed to give the quinoxaline derivative, or substitutions or replacements are made into the quinoxaline nucleus already formed. The former procedure is

---

109. Chardonnens and Venetz, Helv. Chim. Acta, 22, 853 (1939).

110. Loudon, J. Chem. Soc., 537 (1935), 902 (1939), 1525 (1940); Loudon and Shulman, ibid., 1618 (1938), 722 (1941); Holmes and Loudon, ibid., 1521 (1940).

more generally useful since the substitution reactions of quinoxaline are almost entirely confined to the reactive 2- and 3- positions.



XV

Quinoxaline (XV) itself, a feeble monoacid base, may be prepared by the condensation of o-phenylenediamine or its hydrochloride with glyoxal or its sodium sulfite addition product[111] or by condensing catechol and ethylenediamine together to give tetrahydroquinoxaline, which is then oxidised to quinoxaline with alkaline potassium ferricyanide,[112] or by the decarboxylation of quinoxaline-2,3-dicarboxylic acid by heating with alkali.[113] Quinoxaline is stable in the presence of potassium dichromate and boiling sulfuric acid,[111] but it is oxidised to pyrazine-2,3-dicarboxylic acid by alkaline permanganate.[114] Quinoxaline derivatives are reduced to the tetrahydro derivatives by sodium and alcohol[112] or by cata-

---

111. Hinsberg, Ber., 17, 320 (1884); Körner, Ber., 17 Ref., 573 (1884).

112. Merz and Ris, Ber., 20, 1194 (1887).

113. Chattaway and Humphrey, J. Chem. Soc., 645 (1929).

114. Gabriel and Sonn, Ber., 40, 4850 (1907).

lytic hydrogenation over nickel at 160°,[115] and to the dihydroderivatives by stannous chloride, while sodium sulfide has no effect.[116] The hydroquinoxalines may be nitrosated.[112,116]

The condensation of o-aryldiamines with 1,2-dioxo compounds to give quinoxalines is a very general and useful reaction, the reactions being very complete even at low temperatures.[117] Thus benzil or diacetyl yield the corresponding 2,3-diphenyl or 2,3-dimethyl derivatives, respectively; oxalic acid yields 2,3-dihydroxyquinoxalines;[118] dihydroxytartaric acid gives the 2,3-dicarboxylic acids[117] (the mechanism of this reaction is not so simple as thought by the original investigators[119]), and oxalic esters react to give the 2,3-dihydroxy compounds,[120] to mention a few examples. While the primary o-aryldiamines react readily with α-diketones, the N-monoalkyl or arylated bases react to form first the anils, which on treatment with strong acids yield either the so-called stilbazonium salts of the quinoxalines or the quinoxalines themselves, or benzimidazole derivatives by a complex rearrange-

---

115. Eckert and Besler, Ger. patent, 495,101 [Chem. Zentr., 101 II, 313 (1930).

116. Hinsberg and König, Ber., 27, 2185 (1894).

117. (a) Hinsberg, Ann., 237 327 (1887);
(b) Hinsberg and Autenrieth, Ber., 25, 492 (1892).

118. Hinsberg and Pollak, Ber., 29, 784 (1896).

119. Chattaway and Humphrey, J. Chem. Soc., 645 (1929).

120. Meyer and Seelinger, Ber., 29, 2640 (1896).

ment, depending on the substituents of the molecules and the conditions of the reaction.[121]

Pyruvic acid reacts with o-phenylenediamines to give the 2-hydroxy-3-methyl derivatives,[122] and alloxan hydrate readily condenses with them to form alloxazines[123] (the formulae given for the condensation product of alloxan with o-phenylene diamine by Hinsberg[122] does not appear to be correct).

By utilizing 5,6-diaminoquinoline Linsker and Evans[124] were able to prepare pyrido(3,2-f)quinoxaline and its 2,3-dimethyl derivative through condensations with glyoxal and diacetyl, respectively. Their N-oxides were readily prepared by treatment with hydrogen peroxide in glacial acetic acid solution. They were unable to prepare similar derivatives from 7,8-diaminoquinoline, presumably because of the weak basicity of the 8-amino group; however, Renshaw et al.[125] were able to condense it with the more highly reactive phenanthroquinone. From mesoxalic acid and 5,6-diaminoquinoline, 3-hydroxypyrido(3,2-f)quinoxaline-2-carboxylic acid has been prepared.[126]

---

121. Brand and Wild, Ber., 56, 105 (1923).

122. Hinsberg, Ann., 292, 245 (1896).

123. Kuhling, Ber., 24, 2364 (1891).

124. Linsker and Evans, J. Am. Chem. Soc., 68, 874 (1946).

125. Renshaw, Friedmann, and Gajewski, J. Am. Chem. Soc., 61, 3325 (1939).

126. Kauffmann and Zeller, Ber., 50, 1626 (1917).

Camphorquinone has been used to prepare an unusual series of quinoxalines by condensation with substituted o-phenylenediamines.[127] Dimethylcumarandione undergoes condensation with o-phenylenediamine to give 2-hydroxy-3-(2-hydroxy-4,6-dimethylphenyl)quinoxaline by cleavage of the cyclic ether bond, instead of yielding cumarophenazines.[128]

Derivatives of α-dioxo compounds and their reduction products, such as α-isonitrosoketones,[129] α-chloroketones,[117a] γ-bromo-β-oxoesters,[130a] and aryloins[130b] all may yield alkyl quinoxalines when condensed with o-aryldiamines, the extra hydrogen atoms, if any, being removed by reduction at the expense of some component of the reacting mixture. Isonitrosopropiophenone is reported to be an exception in that it does not react with o-phenylquinoxaline.[131] d-Glucose and other sugars react with o-phenylenediamine giving 2-tetrahydroxybutylquinoxalines.[132]

An interesting addition of o-aryldiamines to cyanogen takes place readily to give 2,3-diaminoquinoxaline.[133,134]

---

127. Heckendorn, Helv. Chim. Acta., 12, 50 (1929).

128. Fries and Bartens, Ann., 442, 259 (1925).

129. Böttcher, Ber., 46, 3085 (1913).

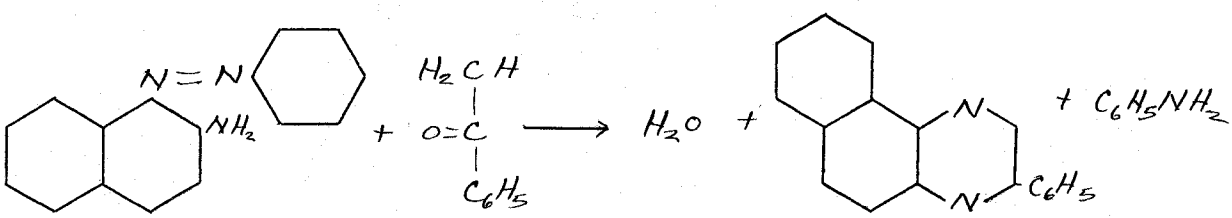
130. (a) Conrad and Hock, Ber., 32, 1208 (1899);
(b) Fischer, Ber., 24, 719 (1891).

131. Bennett and Willis, J. Chem. Soc., 1960 (1928).

132. Kuhn and Bär, Ber., 67, 898 (1934).

133. Bladin, Ber., 18, 666 (1885).

Crippa[135] has reported an unusual reaction whereby various o-aminoazo derivatives react with acetophenone at 165°-170° in the presence of a small amount of hydrochloric acid catalyst forming quinoxalines with the elimination of an arylamine and water as follows:



The quinoxaline may then be oxidised to a 3,4-quinone of β-phenyl-1,2-napthoquinoxaline with chromic acid in glacial acetic acid and condensed with o-phenylenediamine to the corresponding azine.

The o-nitrophenyl-α-aminoaliphatic acids, when reduced, yield 2-substituted-3-hydroxy-dihydroquinoxalines, which are also obtained by the condensation of o-phenylenediamines with α-haloaliphatic acids.[122]

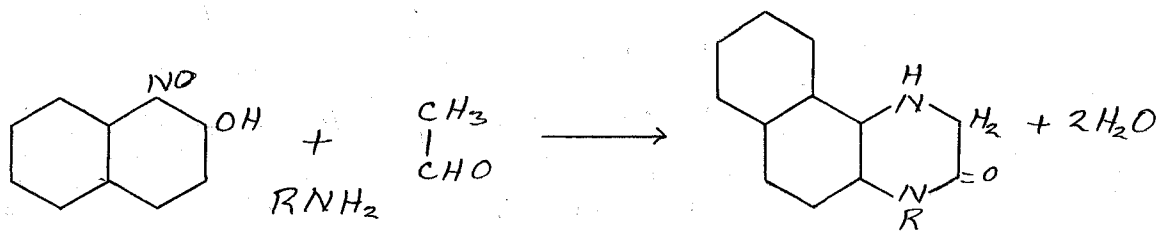
An interesting condensation is that of o-nitrosophenols with acetaldehyde and ammonia or primary aliphatic amines to give hydroxydihydroquinoxalines or oxotetrahydroquinoxalines,

---

134. Hinsberg and Schwantes, Ber., 36, 4039 (1903).

135. Crippa, Gazz. chim. ital., 59, 330 (1929); 60, 301 (1930).

respectively, as follows:[136]



The use of formaldehyde instead of acetaldehyde results in the formation of the bis(2-hydroxydihydro-3-quinoxalyl) ethers.[137]

The condensation of o-aryldiols with alkylenediamines giving tetrahydroquinoxalines has already been mentioned.[112]

It has been possible to resolve the various stereoisomeric bases obtained by the reduction of 2,3-disubstituted quinoxalines to their tetrahydro analogs.[138]

When 2,3-dihydroxyquinoxaline is heated with phosphorus pentachloride, the 2,3-dichloro compound results,[118] which undergoes a number of metathetical transformations. When heated with alcoholic ammonia, it gives a 2-chloro-3-amino derivative;[134] under more drastic conditions the 2,3-diamino derivative is obtained.[139] Likewise the use of ethylamine yields 2,3-bis(N-ethylamino)quinoxaline,[134] and with aryl-

---

136. Lange, Ber., 42, 574 (1909); Lange, Ger. Patent 196,563 /Chem. Zentr., 79 I, 1589 (1908)/.

137. Lange, Ger. Patent 229,127 /Chem. Zentr., 82 I, 179 (1911)/.

138. Bennett and Gibson, J. Chem. Soc., 123, 1570 (1923); Gibson, ibid., 342 (1927).

139. Stevens, Pfister, and Wolf, J. Am. Chem. Soc., 68, 1035 (1946).

amines the corresponding derivatives.[140]

With 2,3-dichloroquinoxaline the sodium alkoxides react to give the 2-alkoxy-3-chloro and the 2,3-dialkoxy derivatives. The former of these can then be treated with ammonia producing 2-alkoxy-3-aminoquinoxaline or a substituted amino compound, such as acetylsulfanilamide, to give the corresponding quinoxaline.[139] The phenoxides react in an analogous fashion.[140]

On the other hand if 2,3-diaminoquinoxaline is heated with aqueous hydrochloric acid, the 2-hydroxy-3-amino and the 2,3-dihydroxyquinoxalines result.[133]

The 2-amino and 2-hydroxy-3-carboxylic acids can be prepared in a number of ways. The application of the Hofmann degradation reaction to ammonium 2-carboxamidoquinoxaline-3-carboxylate, obtained by the action of ammonia on the 2,3-dicarboxylic acid anhydride, yields 2-amino-3-carboxyquinoxaline,[141] which may also be obtained by high-pressure ammonolysis of alloxazine.[142] On the other hand 2-hydroxy-3-carboxyquinoxaline results from hydrolyzing alloxazine with sodium hydroxide.[122,123,132] Hydrolysis of alloxazine with concentrated sulfuric acid gives 2-aminoquinoxaline, which can also be obtained easily by the decarboxylation of the 3-carboxy derivative.[142]

---

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

141. Philips, Ber., 28, 1655 (1895).

142. Weijlard, Tishler, and Erickson, J. Am. Chem. Soc., 66, 1957 (1944).

Bromination of 2,3-dimethylquinoxaline in acetic acid gives not the 5,6,7,8-tetrabromo derivative as has been claimed,[143] but rather, 2,3-di(α-dibromomethyl) quinoxaline by substitution into the active methyl groups. The other α-alkylquinoxalines behave similarly.[144,145]

The active methylene groups of α-alkylated quinoxalines readily condense with various aromatic aldehydes in the same manner as quinaldine to give the styrylquinoxalines.[145]

Ogg and Bergstrom[146] have pointed out that according to the ammonia system of Franklin, quinoxaline may be regarded formally as an ammono glyoxal. They have further pointed out several interesting analogies in support of their thesis and developed several new reactions on that basis. For instance, quinoxaline reversibly adds on two molecules of sodium bisulfite, and it adds on two molecules of hydrocyanic acid to give 1,2,3,4-tetrahydro-2,3-dicyanoquinoxaline. By addition it reacts with two molecules of a Grignard reagent, and on subsequent ammonolysis yields the dl-ammono di-secondary alcohol, tetrahydro-2,3-dialkyl(or aryl)-quinoxaline. With ammonium persulfate, quinoxaline is oxidised to 2,3-dihydroxyquinoxaline, the ammono oxalic acid. With potassium amide, quinoxa-

---

143. Henderson, J. Chem. Soc., 466 (1929).

144. Bennett and Willis, ibid., 1709 (1930).

145. Bennett and Willis, ibid., 1960 (1928).

146. Ogg and Bergstrom, J. Am. Chem. Soc., 53, 245, 1846 (1931).

line gives the complex polyheterocycle, fluorubin, and perhaps polymerized, reduced quinoxaline. This may be regarded as an external ammono Cannizzaro reaction. Fluorubin, incidentally, is best made by the condensation of 2,3-dichloroquinoxaline and 2,3-diaminoquinoxaline.[134] By the same reasoning, 2,3-dichloroquinoxaline is an ammono oxalyl chloride as is emphasized by its preparation from phosphorus pentachloride and the dihydroxy compound;[118] consequently, it reacts with ammono alcohols, viz. amines, giving the ammono esters, such as o-phenyleneethylene oxamidine by condensation with ethylenediamine. (See also ref. 134.) Moreover, like diacid chlorides, 2,3-dichloroquinoxaline reacts with two equivalents of an alkylmagnesium halide, this time to yield an ammono diketone or 2,3-dialkylquinoxaline. (It is a remarkable fact that phenylmagnesium bromide will not react at all.) That the dialkylquinoxalines are indeed ammono α-diketones is further established by the fact that potassium amide in liquid ammonia adds to the enol form of 2,3-dimethylquinoxaline giving a salt which is readily alkylated with alkyl halides just as are the aquo ketones under equivalent circumstances.

Incidentally, it would appear that the condensations of aldehydes with methylquinoxalines might be regarded as Claisen condensations of the ammonia system.

Finally 2,3-diphenylquinoxaline is to be regarded as a substituted ammono benzil, which its synthesis[116] and its

redox interconversions with dihydroquinoxaline and the tetrahydroquinoxalines verify. To complete the analogy, Ogg and Bergstrom were able to secure evidence for an ammono benzilic acid rearrangement of 2,3-diphenylquinoxaline with potassium amide in liquid ammonia, although they did not irrevocably establish the structure of their product as 1,2-dihydro-2,2-diphenyl-3-aminoquinoxaline.

In investigating the chemotherapeutic properties of "sulfa" quinoxalines several have been prepared by methods already outlined.[139,142] 3-Sulfanilamidoquinoxaline has proved very effective in bacterial infections. It has the unusual property of being very slowly eliminated by animals so that an effective blood concentration is easily maintained by infrequent administration.

Spoerri and co-workers[147] have prepared some quinoxaline analogs of pamaquine. No information is available as to their chemotherapeutic activity. A great many cyanine dyes of quinoxaline have been prepared by means employing many of the methods here outlined for investigation as photosensitizers.[148]

In closing it should be noted that condensing o-phenylenediamine with α-diketones is frequently a very good method

---

147. Gawron and Spoerri, J. Am. Chem. Soc., 67, 514 (1945); Mizzoni and Spoerri, ibid., 67, 1652 (1945).

148. Anker and Cook, J. Chem. Soc., 489 (1944); 710 (1942); 394 (1943).

of preparing derivatives of the latter, even when quite complex.[149]

5-and/or 6-Alkyl(Aryl) Substituted 2-Thiouracils

The literature on the pyrimidine derivatives is extremely voluminous. In this field, the laboratories of the department of chemistry of Yale University alone have contributed over one hundred and eighty papers. Their work was begun by Wheeler and subsequently carried on by T. B. Johnson and also by some of his students later working elsewhere. Since the early pioneering work on pyrimidines of Behrend, E. Fischer, and others, the Yale group has been the principal contributor to this field.[150] The interest in the 2-thiouracils until very recently has been largely due to the fact that they can be readily converted by desulfurization to the less readily obtainable uracils, which are of interest because of their intimate connection with many naturally occurring substances.[151]

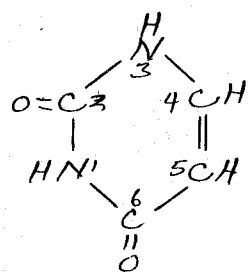
Considerable confusion has existed in the literature due to different systems of numbering the substituents of uracil (XVI). The two most common are that of the Yale group (the one used by Beilstein) (a) and that now preferred by Chemical

---

149. Karrer and Nuess, Helv. Chim. Acta, 28, 1185 (1945).

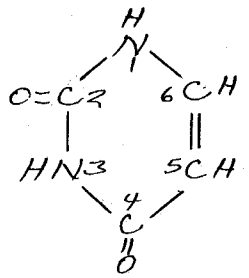
150. For a list of the early papers of this group, see Johnson, Peck, and Ambler, J. Am. Chem. Soc., 33, 758 (1911).

Reviews and Chemisches Zentralblatt (b), which is the one used in this dissertation. It will be noted that the 3- and 5- positions are the same by either method.



(a)

(keto forms)



(b)

XVI

Two general methods have been employed for the preparation of the 5- and 6-alkyl(aryl) substituted 2-thiouracils. Both involve the condensation of β-oxo esters with thiourea,[152] N-substituted thioureas,[153] or S-alkyl-isothioureas[154] giving the 2-thiouracils, N-substituted 2-thiouracils, and the 2-alkylmercapto-4-hydroxypyrimidines, respectively. The first method consists of condensing the two components in the

---

151. For a general discussion and a partial review of the chemistry of the pyrimidines, the reader should consult the chapter written by T. B. Johnson in Gilman's, "Organic Chemistry," 1st Edition, John Wiley and Sons, New York, 1938, and Johnson, T. B. and Hahn, Chem. Rev., 13, 193 (1933).

152. Wheeler and McFarland, Am. Chem. J., 42, 105 (1909).

153. Behrend and Hesse, Ann. 329, 348 (1903).

154. Wheeler and Merriam, Am. Chem. J., 29, 484 (1903).

presence of an acid catalyst such as hydrochloric acid.[155] This method gives much poorer yields and is the less generally applicable of the two. The second method employs sodium ethoxide in alcoholic solution as the condensing agent.[152]

A remarkable variety of β-oxo esters have been employed. For instance, ethyl β-oxopropionate, formylacetic ester, gives 2-thiouracil itself,[156] while the α-substituted formylacetic esters give the corresponding 5-substituted-2-thiouracils with thiourea.[155c] The β- and α,β-substituted β-oxopropionic esters, in general, react forming 6- and 5,6-substituted-2-thiouracil derivatives,[157] the simplest member of this group of esters, acetoacetic ester, forming 6-methyl-2-thiouracil with thiourea.[152] Ethyl γ,γ-diethoxy-β-oxobutyrate has been condensed with thiourea forming 2-thiouracil-6-aldehyde diethylacetal, which can be hydrolyzed to 2-thiouracil-6-aldehyde.[158] This is the only available method for preparing uracil aldehydes. Incidentally, this aldehyde smoothly undergoes the usual Cannizzaro transformation giving 6-hydroxy-

---

155. (a) List, Ann., 236, 3 (1886);
(b) Sonn and Litten, Ber., 66, 1518 (1933);
(c) Johnson and Ambelang, J. Am. Chem. Soc., 60, 2941 (1938).

156. Wheeler and Bristol, Am. Chem. J., 33, 458 (1905).

157. (a) Johnson and Bailey, J. Am. Chem. Soc., 35, 1010 (1913).
(b) Johnson and Hemingway, ibid., 37, 380 (1915).

158. (a) Johnson and Cretcher, ibid., 37, 2144 (1915);
(b) Johnson and Schroeder, ibid., 53, 1989 (1931);
(c) Johnson and Schroeder, ibid., 54, 2941 (1932).

methyl-2-thiouracil and 2-thioörotic acid.[158c] Ethyl α,γ-diethoxy-β-oxobutyrate condenses with thiourea yielding 2-thio-6-ethoxymethyl-5-ethoxy-4-hydroxypyrimidine, and diethyl α-oxo-β-ethoxysuccinate (not isolated) on reaction with ethylisothiourea gave 2-ethylmercapto-5-ethoxy-6-carbethoxy-4-hydroxypyrimidine.[159a] With diethyl α-formylsuccinate and thiourea or alkylisothioureas the corresponding 2-thio or 2-alkylmercapto-5-carbethoxymethyluracils have been obtained.[150]

In some cases, the intermediate ureide to be expected in these condensations of β-oxo esters was isolated. For example, from ethylisothiourea and α-ethylformylacetic ester, some α-ethyl-β-isoethylthioureaacrylic acid was formed.[159b]

Anderson and others[64] in a paper dealing with the preparation of a series of homologous 5-and/or 6-alkyl-2-thiouracils present an evaluation of various methods for preparing β-oxo esters.

In addition to β-oxo esters some closely related compounds have been condensed with thioureas. Ethyl α-cyano-β-ethoxyacrylate gives 2-thio-5-carbethoxy-6-aminopyrimidine by the addition of one amino group of thiourea to the cyano group and elimination of ethanol from the other amino group and the β-ethoxy group of the ester.[160a] The alternate possibility of

---

159. (a) Johnson and Caldwell, ibid., 51, 873 (1929);
(b) Johnson and Menge, J. Biol. Chem., 2, 109 (1906).

160. (a) Johnson and Ambler, J. Am. Chem. Soc., 33, 978 (1911).

a ring closure involving the carbethoxy group of the ester did not take place. (When using alkylisothioureas, the reaction will occur in both ways.[160b]) However, starting with Claisen's ester, diethyl ethoxymethylenemalonate, the latter type of ring closure is the only one possible yielding 2-thio-5-carbethoxyuracil from thiourea,[161a] and the analogous alkylmercaptouracils from alkylisothioureas.[161a,b]

Carbethoxymalonic aldehyde first forms an addition product with ethylisothiourea which is dehydrated by acetic anhydride to 2-ethylmercapto-5-carbethoxypyrimidine.[161c]

Diketene has been reported to give 6-methyluracils with ureas or substituted ureas.[162] It appears certain that thiourea would react likewise.

Sym-di-β-naphthylthiourea has been reported to react slowly with ethyl butyrate in acetic acid in the presence of a little hydrochloric acid to give a small yield of 1,3-di-α-naphthyl-6-methyl-2-thiouracil.[163] This seems to be open to question.

---

160. (b) Johnson, Am. Chem. J., 43, 506 (1909).

161. (a) Ballard and Johnson, J. Am. Chem. Soc., 64 795 (1942).
(b) Wheeler, Johnson, and Johns, Am. Chem. J., 37, 392 (1907).
(c) Dyer and Johnson, J. Am. Chem. Soc., 56, 232 (1934).

162. Boese, Ind. Eng. Chem., 32, 16 (1940).

163. Pozzi-Escot, Anales. quim. labs. cient e ind. E. Pozzi Escot, 35 (1943) [C. A., 38, 1479 (1944)]

Two papers of Johnson and co-workers[157] serve to illustrate most of the common metathetical reactions of thiouracils. 2-Thiouracils are desulfurized to the corresponding uracils, usually very readily, by boiling with dilute chloroacetic acid;[157] an exception is 2-thio-5-carbethoxy-6-aminopyrimidine, which is converted to the carboxymethylmercapto derivative instead.[160a] In alkaline solutions 2-thiouracils react with alkyl halides giving alkylmercapto derivatives, which are hydrolyzed easily with hydrobromic acid or hydrochloric acid to the corresponding uracils. With ammonia or aniline the alkylmercapto derivatives yield the 2-amino or 2-anilino compounds, respectively.

The 4-hydroxy group of 2-alkylmercapto-4-hydroxypyrimidines is replaced by chlorine using phosphorus oxychloride or phosphorus pentachloride. The 4-chloro-2-alkylmercaptouracils are then easily aminated with ammonia giving the thiocytosine analogs, or the chlorine can be replaced by hydrogen through reduction with zinc dust.[159] The chlorine can also be replaced by the thiocyano group on treatment with potassium cyanate.[164] These rhodanides rearrange to the isothiocyanates on boiling with toluene or xylene.

The 2-mercaptopyrimidines (including the 4-hydroxy derivatives) interact with halogens forming addition products which break down on heating, with substitution of the halogen into

---

164. Johnson and Chi, J. Am. Chem. Soc., 52, 1580 (1930); Chi et al., ibid., 54, 2056 (1932); 55, 4181, 4655 (1933); 58, 769, 773 (1936).

the 5- position of the ring.[165a] Chlorine water oxidises alkylmercaptopyrimidines to the alkylsulfonyl derivatives in some cases.[165b]

The nitration of 2-alkylmercaptouracils converts them into the 5-nitrouracils.[166a] This may involve the intermediate formation of the uracils, which are obtained by the action of dilute, hot nitric acid on 2-alkylmercaptouracils. The uracils may then be nitrated to 5-nitrouracils by concentrated nitric and sulfuric acid mixtures.[166b]

Johnson found that 2-thiothymine aldehyde[167] condenses with dimethylaniline in the presence of zinc chloride forming the leuco base, 6-/p,p'-bis(dimethylamino)benzohydryl/-5-methyl-2-thiouracil.[168]

Ganapathi[169] has observed that diazotized 2-N'-sulfanilamidothiazole couples with 4-amino-2-thiouracil to form 4-amino-5-/4'-(2-thiazolyl)sulfamylphenylazo/thiouracil.

---

165. (a) Johnson and Joyce, ibid., 38, 1557 (1916).
(b) Sprague and Johnson, ibid., 57, 2252 (1935); 60, 1622 (1938).

166. (a) Johnson, Johns, and Heyl, Am. Chem. J., 36, 160 (1906).
(b) Robinson and Tomlinson, J. Chem. Soc., 1283 (1935).

167. Johnson and Cretcher, J. Biol. Chem., 26, 99 (1916).

168. Johnson, J. Am. Chem. Soc., 51, 1274 (1929).

169. Ganapathi, Proc. Indian Acad. Sci., 12A, 274 (1940).

III. EXPERIMENTAL

Unless otherwise specified all compounds used were of the highest purity commercially obtainable. All melting and boiling points are uncorrected. All analyses for nitrogen were performed by the micro Dumas method except where otherwise noted. The sulfur analyses were made by the macro Parr bomb procedure.

A. Diaryl Sulfides and Sulfones

m-Chlorothiophenol

Following a modification of Leuckart's method[170] for converting arylamines to thiophenols through the S-arylxanthates, 63.75 g. (0.5 mole) of m-chloroaniline, dissolved in 120 ml. of concentrated hydrochloric acid and 300 ml. of water, was cooled in ice with vigorous stirring to get a fine suspension of the hydrochloride and diazotized by the slow addition with stirring of saturated sodium nitrite solution under the surface of the mixture until a slight excess was present (starch-iodide paper).

Then the clear, red diazonium solution, kept at 0°, was added dropwise over a one hour period to a solution of 160 g. (1.0 mole) of potassium ethyl xanthate stirred vigorously and

---

170. Leuckart, J. prakt. Chem., [2] 41, 179 (1890); Schwarzenbach and Egli, Helv. Chim. Acta., 17, 1176 (1934).

maintained at 80° to facilitate decomposition of the diazonium xanthate ester. The decomposition of the intermediately formed diazo ester was quite violent, particularly at first, occurring with loud reports and flashes of flame unless the rate of addition was kept slow. After the addition was complete, heating and stirring were continued for two hours to complete the decomposition of the diazo ester.

The heavy, insoluble, red oil was separated and saponified by refluxing for six hours with 84 g. (1.5 moles) of potassium hydroxide dissolved in 300 ml. of ethanol and 75 ml. of water. During the course of the hydrolysis another 20 g. of potassium hydroxide and 300 ml. of ethanol were added. Finally, 400 ml. of ethanol was distilled off, the residue diluted to 1 l. volume with water, and extracted with ether. The ether extract was dried over anhydrous sodium sulfate, filtered, and flashed into a 125 ml. modified Claisen flask. On fractional distillation, 47 g. (65%) of slightly opalescent, colorless liquid distilling at 91°-92.5°/15 mm. was obtained as the main fraction. At 176°-183°/0.4 mm., 12.4 g. of pale, yellowish liquid distilled (probably the disulfide). (Reported for the thiophenol,[171] b.p./760 mm. 205°-207°.)

It should be mentioned that unless the temperature of the potassium ethyl xanthate solution is maintained above 60° as

---

171. Daccomo, Jahresbericht über die Fortschritte der Chemie, 1375 (1891) /Beil., 6, 326/.

the diazonium salt solution is added, undecomposed diazo ester may accumulate and then detonate with great violence.[172]

o-Chlorothiophenol

Following the same procedure as that used in the preparation of m-chlorothiophenol, 76.5 g. (0.6 mole) of o-chloroaniline dissolved in 139 ml. (1.25 moles) of concentrated hydrochloric acid and 350 ml. of water was diazotized. The diazonium salt in this case was not completely soluble. Unusually loud reports accompanied the decomposition of the intermediate diazonium ester as the diazonium salt was added to the 192 g. (1.2 moles) of potassium ethyl xanthate dissolved in 600 ml. of water.

The crude product, on distillation, gave 58 g. of slightly cloudy, colorless liquid boiling at 87°-89°/14 mm. (67%) and a few grams of high boiling residue. (Reported:[171] b.p. 205°-206°/760 mm.)

p-Chlorothiophenol

By the same procedure as above 35.5 g. of p-chlorothiophenol[171] was obtained from 63.75 g. (0.5 mole) of p-chloroaniline (49%).

---

172. Hantzsch and Freese, Ber., 28, 3240 (1895).

4-Isopropylbenzenesulfonyl Chloride

The method of Huntress and co-workers[173] for making derivatives of alkylbenzenes through their sulfonamides was adapted for large scale preparation. By this means, 100 g. (0.835 mole) of cumene dissolved in 500 ml. of chloroform in a three-necked flask and cooled to 0° in an ice-bath was treated with stirring with 500 g. (4.3 moles) of freshly distilled chlorosulfonic acid by dropwise addition. After the initial evolution of hydrogen chloride had subsided, the mixture was allowed to warm to room temperature. The contents of the flask was poured upon crushed ice, the chloroform layer separated and washed with ice water, and the solvent evaporated. An estimate on the yield of the crude sulfonyl chloride, which has never been isolated in pure form, was made by converting a small portion to the sulfonamide. The purified, white platelets of p-isopropylbenzenesulfonamide melted at 105.5°-106.5°.[173a] The amount formed indicated the chlorosulfonation of the cumene was substantially complete.

p-Isopropylthiophenol

Concentrated sulfuric acid, 293.5 g. (2.84 moles), was added to 900 g. of ice in a 2 l. three-necked flask, and the mixture kept at -5° to 0° with an ice-salt bath while 91 g.

---

173. (a) Huntress and Autenrieth, J. Am. Chem. Soc., 63, 3446 (1941);
(b) Huntress and Carten, ibid., 62, 511 (1940).

(0.414 mole) of the crude sulfonyl chloride was run in with vigorous stirring. Then 147 g. (2.10 moles) of zinc dust (90%) was added as rapidly as maintaining the temperature at 0° would allow (approx. 30 min.). After one and one-half hours stirring at 0°, the mixture was allowed to warm to room temperature and finally refluxed for five hours, at which time it became clear. The mixture was steam distilled as long as an oil separated from the distillate. The chilled distillate was extracted with ether, and the extract dried over anhydrous sodium sulfate. After evaporation of the ether, the residue was distilled through a twelve inch Vigreaux column. With no forerun, 40 g. of colorless, mobile oil distilling at 100°-104.5° (14 mm.) was obtained (63.5%).

N_D^{20} 1.5542; d_4^{20} 1.0009; M_D calcd. 47.9, found 48.7.[174]

Anal. Calcd. for $C_9H_{12}S$: S, 21.1%.

Found: S, 21.2%.

3'-Methyl-4-nitrodiphenyl Sulfide

All of the substituted nitrodiphenyl sulfides were made by the reaction of a sodium mercaptide with a nitrohalobenzene. The following procedure given in detail is illustrative of the technique employed with the remaining compounds of this series, which will subsequently be described only briefly.

To a solution of 62.g. (0.5 mole) of m-thiocresol in 400 ml. of absolute ethanol was added 11.5 g. (0.5 atom) of sodium.

---

174. The experience of Suter and Hansen, J. Am. Chem. Soc., 54, 4101 (1932), indicates that an exaltation in the atomic refraction of sulfur is common. The calculated value was computed from Eisenlohr's figures.

When the sodium had dissolved, a solution of 101 g. (0.5 mole) of p-nitrobromobenzene in 700 ml. of absolute methanol was added all at once. (p-Nitrochlorobenzene is equally satisfactory.) The mixture was refluxed for three hours. (Mechanical stirring is frequently necessary to prevent severe bumping.) The deposited sodium bromide was filtered off, the solution cooled, and the resulting crystals removed by filtration. Two more crops of crystals were obtained on concentrating the mother liquors. Recrystallization from ethanol gave a total of 106.2 g. (87%) of compact, yellow crystals melting at 47°.

On a smaller run (0.2 mole) employing a longer reaction time, in which the product was worked up by pouring the reaction mixture over cracked ice and filtering, considerable tar was obtained with the product. After several recrystallizations, a total of 26.25 g. (53.5%) of product melting at 47° was obtained.

Anal. Calcd. for $C_{13}H_{11}O_2NS$: N, 5.72%.
Found: N, 5.75%.

2-Nitrodiphenyl Sulfide

From 22 g. (0.2 mole) of thiophenol and 4.6 g. (0.2 atom) of sodium in 200 ml. of absolute ethanol reacted with 40.4 g. (0.2 mole) of o-nitrobromobenzene in 200 ml. of ethanol for thirty minutes, 43.5 g. of product was isolated following drowning in ice and water, filtration, and crystallization (95%).

Melting point, 80.5°. (Reported: 77°.[175] 80.2°.[81])

4-Nitrodiphenylsulfide

On a 0.2 mole run made in the same manner as the one just preceding, but using p-nitrobromobenzene and a three-hour reaction time, 39.5 g. of a pale-yellow, crystalline product, melting point 55°, was obtained (86%). (Reported: 55°,[91] 54.4°.[81])

A run of the same size, in which sodium hydroxide was substituted for sodium in preparing the thiophenoxide, gave a yield of only 35.5%.

2'-Methyl-2-nitrodiphenyl Sulfide

From 24.8 g. (0.2 mole) of o-thiocresol in 200 ml. of ethanol and an equivalent amount of sodium reacting with 0.2 mole of o-nitrobromobenzene in 200 ml. of ethanol for thirty minutes, on working up the crude product, 41 g. (84%) of brownish-yellow crystals was obtained, melting at 87°-88°. (Reported: 86°-87°,[175] 86°.[176])

3'-Methyl-2-nitrodiphenyl Sulfide

For four hours, 0.2 mole each of sodium m-thiocresolate and o-nitrobromobenzene were refluxed in 400 ml. of absolute ethanol. After pouring the mixture over ice, filtering, and

---

175. Mauthner, Ber., 39, 3597 (1906).

176. Varma et al., J. Indian Chem. Soc., 19, 354 (1942).

crystallizing twice from boiling ethanol, a yield of 44.5 g. (91%) of product melting at 86°-86.5° was obtained.[177]

Anal. Calcd. for $C_{13}H_{11}O_2NS$: S, 13.1%

Found: S, 13.3%.

4'-Methyl-2-nitrodiphenyl Sulfide

Two-tenths mole of sodium p-thiocresolate and 0.2 mole of o-nitrobromobenzene were refluxed together in 500 ml. of absolute ethanol for one hour. Then the mixture was poured into 1.5 l. of ice and water, filtered, and twice crystallized from ethanol to give 45.5 g. (93%) of pale-yellow needles, which melted at 89°-90°. (Varma[177] gives 87.5° as his melting point.)

Anal. Calcd. for $C_{13}H_{11}O_2NS$: S, 13.1%

Found: S, 13.0%.

2'-Methyl-4-nitrodiphenyl Sulfide

When 0.2 mole of sodium o-thiocresolate and the equivalent amount of p-nitrobromobenzene were allowed to interact for three hours in 500 ml. of boiling absolute ethanol and then processed by drowning in ice water, only an uncrystallizable oil resulted. Therefore, the aqueous suspension was extracted with ether and the extract dried, filtered, and

---

177. After this compound had already been synthesized and analyzed by the author, a report of its preparation by Varma and co-workers, op. cit., became available.

evaporated. The residue was distilled at 170°-176°/1.0 mm. The solidified distillate was twice recrystallized from methanol giving 29.5 g. (60%) of product melting at 64°-65°.

Anal. Calcd. for $C_{13}H_{11}O_2HS$: S, 13.1%.

Found: S, 13.1%.

4'-Methyl-4-nitrodiphenyl Sulfide

For one and one-half hours, 0.2 mole of sodium p-thiocresolate, prepared as usual, and an equivalent of p-nitrobromobenzene were refluxed in 400 ml. of absolute ethanol. On working up, beautiful, pale-yellow crystals were obtained in the amount of 44 g. (90%). Melting point, 80°-81°. (Reported:[178] 81.5°.)

2'-Chloro-4-nitrodiphenyl Sulfide

In 350 ml. of absolute ethanol, 0.15 mole of the thiophenolate prepared from 21.7 g. of o-chlorothiophenol and 3.45 g. of sodium was refluxed with 23.6 g. (0.15 mole) of p-nitrochlorobenzene for three hours. The sodium chloride was filtered off, and the solution concentrated and cooled. After two crystallizations from ethanol the melting point was constant at 113°-114°. Yield, 31.9 g. (80%).

Anal. Calcd. for $C_{12}H_8O_2NClS$: S, 12.06%.

Found: Cl, 12.24%.

---

178. Law and Johnson, J. Am. Chem. Soc., 52, 3623 (1930).

3'-Chloro-4-nitrodiphenyl Sulfide

Sodium m-chlorothiophenolate (0.15 mole) and 0.15 mole of p-nitrochlorobenzene were refluxed for three hours in 350 ml. of absolute ethanol. After filtering off the sodium chloride and concentrating the solution, a mass of fine, yellow crystals was obtained. After three crystallizations from ethanol the melting point was constant at 71°-71.5°. Yield, 29 g. (73%).

Anal. Calcd. for $C_{12}H_8O_2NClS$: S, 12.1%.

Found: S, 12.3%.

4'-Chloro-4-nitrodiphenyl Sulfide

From 14.45 g. (0.1 mole) of p-chlorothiophenol, 2.3 g. (0.1 atom) of sodium, and 20 g. (0.1 mole) of p-nitrobromobenzene, 18 g. (68%) of yellow, crystalline product was obtained after crystallization from ethanol and then from methanol. The melting point was 83°-84°.[179]

Anal. Calcd. for $C_{12}H_8O_2NClS$: S, 12.06%.

Found: S, 12.13%.

4'-Isopropyl-4-nitrodiphenylsulfide

In 250 ml. of absolute ethanol 15.2 g. (0.1 mole) of sodium p-isopropylthiophenolate and 20.2 g. (0.1 mole) of p-nitrobromobenzene were refluxed for two hours. The salt

---

179. The preparation of this compound was reported by Burton and Hoggarth (ref. 37) after the above synthesis had been completed. They give its melting point as 88°; however, repeated crystallization of the above product did not raise its melting point above 84°.

was removed by filtration, and the solution was concentrated. On cooling, most of the material oiled out and solidified, then 5.8 g. of pale yellow plates, melting point 40°-42° crystallized out. After two recrystallizations of the product from dilute methanol, 17.7 g. (65%) of pure product melting at 47.5°-48.5° was obtained.

On another run of 0.066 mole, the crude product could not be induced to crystallize. It was distilled under reduced pressure at 173°-180°/0.3 mm. yielding 13.2 g. (73.5%) of clear, yellow oil, which slowly crystallized. It was used without further purification.

Anal. Calcd. for $C_{15}H_{15}O_2NS$: S, 11.75%.
Found: S, 11.9%.

4'-Methoxy-4-nitrodiphenyl Sulfide

Nine g. (0.0643 mole) of very crude p-methoxythiophenol was converted to its sodium salt in 200 ml. of absolute ethanol, reacted with 13 g. (0.065 mole) of p-nitrobromobenzene for nine hours, and poured into ice water and filtered. After two crystallizations of the precipitate from ethanol with intervening treatments with Norit, 7 g. (42%) of product was obtained melting at 68°. (Reported:[180] 71°.)

---

180. Johnson and Bass, J. Am. Chem. Soc., 52, 1146 (1930).

3'-Methyl-2,4-dinitrodiphenyl Sulfide

Two-tenths mole of sodium m-thiocresolate in 200 ml. of absolute ethanol was treated with 40.5 g. (0.2 mole) of 2,4-dinitrochlorobenzene in 300 ml. of hot absolute ethanol. Almost immediately the solution became dark and sodium chloride began to precipitate. After refluxing for thirty minutes, the solution was concentrated and cooled. The product obtained was so tarry that it was abandoned.

In another run of the same size and dilution the thiophenolate solution was allowed to cool to room temperature before mixing with the hot 2,4-dinitrochlorobenzene solution. The reaction appeared to be complete almost instantaneously. The mixture was heated to boiling, quickly filtered, and cooled. The product, which showed a marked tendency to oil out of solution, was twice recrystallized from boiling ethanol yielding 37.3 g. (64.5%) of yellow crystals melting at 99.5°-100.5°.

Anal. Calcd. for $C_{13}H_{10}O_4N_2S$: S, 11.00%.
Found: S, 11.13%.

3'-Chloro-2,4-dinitrodiphenyl Sulfide

To 0.1 mole of sodium m-chlorothiophenolate dissolved in 100 ml. of absolute ethanol, an equivalent of 2,4-dinitrochlorobenzene in 150 ml. of the same solvent was added, and the mixture was refluxed for fifteen minutes, filtered, concentrated, and cooled. Purification of the crude product by

crystallization was very slow and difficult. The compound seemed to decompose somewhat on crystallization. After six recrystallizations from ethanol, the melting point of the product was steady at 108°-109°. Yield, 12 g. (38.5%).

Anal. Calcd. for $C_{12}H_7O_4N_2ClS$: S, 10.32%.
Found: S, 10.44%.

4'-Chloro-2,4-dinitrodiphenyl Sulfide

When 0.1 mole of sodium p-chlorothiophenolate, prepared in 100 ml. of absolute ethanol, and 0.1 mole of 2,4-dinitrochlorobenzene were mixed, vigorous reaction immediately ensued. After refluxing for fifteen minutes, filtering, and cooling, fluffy, bright yellow crystals of product crystallized from the solution. After one recrystallization from ethanol, 21 g. (68%) of the compound melting sharply at 121°-122° was secured.

Anal. Calcd. for $C_{12}H_7O_4N_2ClS$: S, 10.32%.
Found: S, 10.45%.

4'-Isopropyl-2,4-dinitrodiphenyl Sulfide

One-tenth mole (15.2 g.) of p-cumenethiol in 100 ml. of absolute ethanol was converted to the mercaptide with 0.1 atom of sodium, mixed with 20.25 g. (0.1 mole) of 2,4-dinitrochlorobenzene in 150 ml. of absolute ethanol, refluxed ten minutes, drowned in 1 l. of ice and water, and filtered. The gummy residue was twice crystallized from methanol giving 17.3 g. (55%) of deep yellow crystals melting at 95.5°-96.5°.

(This compound displayed a strong tendency to oil out of solution. Methanol proved to be a much better solvent than ethanol.)

On another run, carried out in the same way except the salt was merely filtered from the reaction mixture instead of being removed by drowning in ice water, provided 13.1 g. (41%) of pure material on processing.

Anal. Calcd. for $C_{15}H_{14}O_4N_2S$: S, 10.1%.
Found: S, 10.1%.

2'-Chloro-4-nitrodiphenyl Sulfone

Hydrogen peroxide (30%) is the reagent of choice for oxidizing sulfides to sulfones. This reagent was used for the preparation of all the sulfones prepared in the course of these investigations. The following procedure given in detail is illustrative of that followed in each case. The preparation of the remaining members of the series will be only briefly described.

Fifteen g. (0.0566 mole) of 2'-chloro-4-nitrodiphenyl sulfide dissolved in 100 ml. of warm glacial acetic acid was treated with 25 ml. of Perhydrol (30% hydrogen peroxide) and heated on the steam plate for one hour. On dilution with water to incipient crystallization and cooling, pale yellow, well-formed crystals deposited. The crystals were filtered off, dried, and recrystallized from ethanol-benzene (1:1). The product, which melted at 160°-161°, weighed 16 g., a 95%

yield. Frequently, as in this case, the sulfone when first obtained from the acetic acid solution is pure, requiring no further crystallization.

Anal. Calcd. for $C_{12}H_8O_4NClS$: S, 10.77%.
Found: S, 10.86%.

4-Nitrodiphenyl Sulfone

From 23.1 g. (0.1 mole) of 4-nitrodiphenyl sulfide in 200 ml. of glacial acetic acid and 30 g. (ca. 0.25 mole) of Perhydrol, a total of 26 g. (98%) of product was obtained after recrystallization from dilute ethanol. Melting point, 143°. (Reported:[181] 143°, by a different method of preparation.)

2'-Methyl-2-nitrodiphenyl Sulfone

From 24.5 g. (0.1 mole) of the sulfide and an excess of Perhydrol, 22.2 g. (80%) of product as large, yellow, cubic crystals was obtained following recrystallization from ethanol.

Anal. Calcd. for $C_{13}H_{11}O_4NS$: S, 11.6%.
Found: S, 11.7%.

3'-Methyl-4-nitrodiphenyl Sulfone

One-tenth mole of the sulfide, on oxidation with Perhydrol in glacial acetic acid followed by two recrystallizations from dilute ethanol, yielded 25.2 g. (91%) of fine, yellow needles

---

181. Ullmann and Pasdermadjian, Ber., 34, 1154 (1901).

melting at 121°-122°.

Anal. Calcd. for $C_{13}H_{11}O_4NS$: S, 11.6%.

Found: S, 11.6%.

4-Methyl-4-nitrodiphenyl Sulfone

This sulfone was prepared from 0.1 mole of the sulfide in 91% yield. Melting point, 171°-172°. (Reported:[104] 170°, prepared by a different method.)

3'-Chloro-4-nitrodiphenyl Sulfone

Fifteen g. (0.0565 mole) of the sulfide in 90 ml. of glacial acetic acid was oxidised to the sulfone with 25 ml. of Perhydrol. The yield was 16.3 g. or 97%. After two recrystallizations from boiling ethanol the melting point was 142°-144°.

Anal. Calcd. for $C_{12}H_8O_4NClS$: S, 10.8%.

Found: S, 10.7%.

4'-Chloro-4-nitrodiphenyl Sulfone

Five g. (0.0188 mole) of 4'-chloro-4-nitrodiphenyl sulfide in 50 ml. of glacial acetic acid was oxidised with 5 ml. of Perhydrol. On crystallization, 5 g. (90%) of fine, white needles was obtained melting at 182°-183°.[182]

Anal. Calcd. for $C_{12}H_8O_4NClS$: N, 4.72%.

Found: N, 4.74%.

---

182. Burton and Hoggarth (ref. 37) published an account of the preparation of this compound after the above work had been completed; however, they list the melting point of the compound as 154°.

4'-Isopropyl-4-nitrodiphenyl Sulfone

From 15.3 g. (0.055 mole) of the sulfide and 31.8 g. (0.28 mole) of Perhydrol heated in 100 ml. of glacial acetic acid, thick, pale yellow needles of the sulfone were obtained on concentrating, diluting, and cooling the solvent. This sulfone showed a marked tendency to oil out of solution. Following three recrystallizations from ethanol, the melting point of the 14.5 g. (87%) of product was 109°-111°. When recrystallized from a mixture of benzene and ligroin, the melting point was likewise 109°-111°.

Anal. Calcd. for $C_{15}H_{15}O_4NS$: S, 10.5%.
Found: S, 10.7%.

3'-Methyl-2,4-dinitrodiphenyl Sulfone

Eighteen g. (0.062 mole) of the sulfide in 175 ml. of glacial acetic acid was heated for several hours with 35 g. (0.31 mole) of Perhydrol. On cooling 17.8 g. (90%) of beautiful, pale yellow crystals were deposited. After two recrystallizations from glacial acetic acid, the melting point was 128°-129°.

Anal. Calcd. for $C_{13}H_{10}O_6N_2S$: S, 9.97%.
Found: S, 10.14%.

5'-Chloro-2,4-dinitrodiphenyl Sulfone

From 5.8 g. (0.0187 mole) of the sulfide and 10 ml. of Perhydrol in glacial acetic acid, a product melting at 142°-

144° was obtained; however, after being recrystallized from ethanol-benzene (5:1), it melted at 155°-156°. Yield, 6.2 g. (97%).

Anal. Calcd. for $C_{12}H_7O_6N_2ClS$: S, 9.36%.
Found: S, 9.38%.

4'-Chloro-2,4-dinitrodiphenyl Sulfone

Ten g. (0.0322 mole) of the sulfide oxidised by 17 g. (0.15 mole) of Perhydrol gave 10.3 g. (94%) of massive, white crystals after recrystallization from ethanol or benzene, melting at 168°. (Reported:[104] 168°, made by another method)

4'-Isopropyl-2,4-dinitrodiphenyl Sulfone

The treatment of 17.3 g. (0.0545 mole) of the sulfide with 30.9 g. (0.272 mole) of Perhydrol in 135 ml. of glacial acetic acid on the steam plate for one and one-half hours, followed by cooling, gave crystals only after violent scratching. Concentration of the mother liquor gave only oily material which could not be induced to crystallize. After two recrystallizations of the crystalline portion from dilute ethanol, 10 g. (53.5%) of product melting at 118°-119° was obtained.

Anal. Calcd. for $C_{15}H_{14}O_6N_2S$: S, 9.16%.
Found: S, 9.18%.

3'-Methyl-4-aminodiphenyl Sulfide

The aminodiphenyl sulfides and sulfones hereafter described were prepared by reduction of the corresponding nitro compounds either with tin and hydrochloric acid or by catalytic reduction with molecular hydrogen over Raney nickel catalyst. The latter method was found to be much the better of the two. The following two procedures given in detail indicate the general technique followed in most of the succeeding preparations.

Tin and hydrochloric acid reduction method. Twenty g. (0.0816 mole) of 3'-methyl-4-nitrodiphenyl sulfide dissolved in 150 ml. of hot ethanol was placed in a three-necked flask of a suitable size with 30 g. mossy tin. Then 125 ml. of concentrated hydrochloric acid was added slowly with stirring. After refluxing one hour, the solution was poured into cracked ice, and 200 ml. of 50% sodium hydroxide solution was stirred in. The precipitate was filtered off, dried, and extracted with boiling ethanol. On cooling, fine, white platelets separated out. The product was recrystallized from dilute ethanol to a constant melting point of 72.5°-73°. The yield was 14 g. (80%).

All of the amino derivatives were very soluble in ethanol, but they could be crystallized quite satisfactorily from dilute ethanol, although considerable care was sometimes required to induce crystallization rather than oiling out.

Anal. Calcd. for $C_{13}H_{13}NS$: S, 14.9%.

Found: S, 14.8%.

Catalytic reduction method. A suspension of 61.25 g. (0.25 mole) of 3'-methyl-4-nitrodiphenyl sulfide in 300 ml. of absolute ethanol together with 4-5 g. of Raney nickel catalyst was shaken at room temperature under 1-4 atm. pressure in a standard Parr low-pressure hydrogenation apparatus until the required amount of hydrogen had been absorbed (1-2 hours). The solution, filtered free of catalyst, was concentrated to 150 ml., diluted with 20 ml. of water, and cooled. On seeding, a mass of crystals formed. On filtering and drying, 47 g. of white plates melting at 72°-73° was obtained (87.5%).

2-Aminodiphenyl Sulfide

According to the method of Cullinane and Davies,[83] 20 g. (0.0865 mole) of 2-nitrodiphenyl sulfide, 30 g. (0.538 atom) of iron filings, 0.3 g. of ferric chloride, and 30 ml. water were digested for three hours on a steam bath, poured into 1.1. of boiling 1:10 hydrochloric acid, cooled, and filtered. The free amine, recovered from the hydrochloride, after two crystallizations from ligroin, amounted to 8.7 g. (50%). It darkened rapidly in the air. Melting point, 43°. (Reported:[83] 35°.)

2'-Methyl-2-aminodiphenyl Sulfide

Twenty g. (0.0816 mole) of the nitro compound was reduced

with tin and hydrochloric acid in alcoholic solution. On crystallization from ethanol, of the product obtained on making the reduction mixture alkaline, 13 g. (74.5%) of iridescent, white plates melting at 89°-90.5° was obtained.

Anal. Calcd. for $C_{13}H_{13}NS$: S, 14.9%.
Found: S, 14.9%.

3'-Methyl-2-aminodiphenyl Sulfide

Twenty g. (0.0816 mole) of the nitro compound was reduced, in the way described, with tin and hydrochloric acid. The crude product extracted from the tin-containing precipitate would not crystallize; hence it was transferred to a distilling flask and the solvent evaporated. The residue distilled at 174°-177°/1 mm. giving 14 g. (80%) of colorless oil, which rapidly turned a deep blue on exposure to the air.

Sp. Gr.$^{20}_{20}$ 1.159; N_D^{20} 1.6518; M_D calcd. 67.31, found 67.8.

Anal. Calcd. for $C_{13}H_{13}NS$: S, 14.9%.
Found: S, 14.83%.

4'-Methyl-2-aminodiphenyl Sulfide

Tin and hydrochloric acid reduction. Twenty g. (0.0816 mole) of the nitro compound was reduced as described above with tin and hydrochloric acid. Great difficulty was encountered in purifying the alcoholic extract of the alkali-precipitated, crude base. Colloidal suspensions of the amine-tin complex

formed and the amine would not crystallize. Finally it was distilled at 159°-164°/1 mm., coming over as a colorless liquid. N_D^{20} = 1.6586. While its density was being determined, it suddenly crystallized in the pycnometer. After being twice crystallized from ethanol at -80°, 8.8 g. (50%) of long, colorless needles were obtained melting at 49°.

From a 15 g. (0.0613 mole) run made in the same manner as the first, it was possible to isolate a crystalline product melting at 48° without resorting to distillation.

Catalytic reduction method. From 5 g. (0.0204 mole) of the nitro sulfide reduced catalytically under 3 atm. pressure of hydrogen with "wet" Raney nickel catalyst, no difficulty was encountered in isolating beautiful, white needles of product. The yield was 3.5 g. (80%) melting at 48.5°-49°.

Anal. Calcd. for $C_{13}H_{13}NS$: S, 14.9%.
Found: S, 15.04%.

4-Aminodiphenyl Sulfide

By tin and hydrochloric acid reduction, 20 g. (0.0865 mole) of the nitro compound was reduced with tin and hydrochloric acid giving 13 g. (74%) of product without difficulty, melting at 95°. (Reported:[91] 95°.)

By catalytic reduction, a 10 g. (0.0422 mole) portion of p-nitrodiphenyl sulfide, prepared by A. H. Seidel working in these laboratories, suspended in 200 ml. of absolute ethanol

with 1 g. of "wet" Raney nickel catalyst was shaken under 3 atm. pressure of hydrogen for twenty-four hours. Only a negligible amount of hydrogen was taken up. The suspended material was dissolved in hot ethanol, filtered, and cooled. A small quantity of flat, greenish-gold platelets melting at 117°-118° was obtained. This product proved to be identical with a sample of bis(p-phenylmercapto)azobenzene, melting point, 117°-118°, prepared by José Iriarte[183] of these laboratories, as shown by a mixed-melting point determination.

Fifty g. (0.2165 mole) of very pure 4-nitrodiphenyl sulfide kindly supplied by Iriarte was suspended in 300 ml. of absolute ethanol with 5-10 g. of Raney nickel catalyst and shaken under 3 atm. of hydrogen until the required amount had been absorbed (three hours). On concentrating and cooling the filtered solution, 38.8 g. (89%) of white platelets of amine melting at 94° was obtained.

2'-Methyl-4-aminodiphenyl Sulfide

Thirty g. (0.122 mole) of the nitro compound was reduced with tin and hydrochloric acid. Freeing the crude product from tin-containing impurities was extremely difficult. Treating the solution of crude product with Norit, filtering, cooling, and refiltering was repeated over ten times before a pure product was secured. The yield was 10.3 g. (39%) of large

183. Iriarte, José, Unpublished studies.

white crystals melting at 51.5°-52°. (Reported:[87b] 50°, by a different method of preparation.)

4'-Methyl-4-aminodiphenyl Sulfide

Five g. (0.0204 mole) of the sulfide was quickly and amoothly reduced catalytically with hydrogen. From the filtered and concentrated solution, diluted with water and cooled, 3.4 g. (78%) of long, well-formed needles of amine was obtained melting at 72°-73°. (Reported:[178] 73.5°, by stannous chloride reduction.)

2'-Chloro-4-aminodiphenyl Sulfide

Twelve g. (0.045 mole) of nitro sulfide was easily reduced catalytically with hydrogen. After two crystallizations from dilute ethanol, 8.3 g. (78%) of long, white needles melting at 77°-78° was obtained.

Anal. Calcd. for $C_{12}H_{10}NClS$: S, 13.61%
Found: S, 13.56%

3'-Chloro-4-aminodiphenyl Sulfide

Eleven g. (0.0415 mole) of the nitro compound was reduced catalytically in ethanol solution. The great insolubility of the intermediate products made the reduction rather slow. From the filtered, concentrated, and water-diluted solution, crystals were obtained by cooling to -80°. The product so obtained was twice recrystallized from dilute ethanol, melting point, 72°-72.5°. Yield, 8 g. (82%).

Anal. Calcd. for $C_{12}H_{10}NClS$: S, 13.61%.
Found: S, 13.73%.

4'-Chloro-4-aminodiphenyl Sulfide

Ten g. (0.0377 mole) of the sulfide was catalytically reduced with hydrogen. From the reaction solution, 7 g. (79%) of a fine, white powder melting unchanged at 60°-61° was obtained.

Anal.[184] Calcd. for $C_{12}H_{10}NClS$: S, 13.61%.
Found: S, 13.80%.

4'-Isopropyl-4-acetaminodiphenyl Sulfide

Nine g. (0.033 mole) of the crude nitro compound was reduced catalytically. The isolated product was a viscous oil, which was distilled *in vacuo*. Since a rather unsatisfactory purification was obtained on distillation, it was acetylated with acetic anhydride in glacial acetic acid solution. This product was recrystallized several times from dilute ethanol without change in its double melting point. The compound first melted at 93.5°-94.5°, then solidified, and finally remelted at 108°-109°. The change from the lower to higher melting form is evidently irreversible under some conditions, because if a sample is once heated to 110° and allowed to solidify, it may exhibit only the higher of the two melting

184. This compound is listed in the literature, German Patent 632,572, /*Chem. Zentr.*, 107, II, 3148 (1936)/, but no data on its properties nor analysis are given.

points thereafter. Yield, 4.2 g. or 45%.

Anal. Calcd. for $C_{17}H_{19}ONS$: S, 11.24%.
Found: S, 11.40%.

3'-Methyl-2,4-diaminodiphenyl Sulfide

Twelve g. (0.0414 mole) of the dinitro sulfide was easily reduced catalytically with hydrogen. After three crystallizations from dilute ethanol, beautiful, large, lavender crystals melting at 112°-112.5° were obtained. Yield, 8.2 g. (865%).

Anal. Calcd. for $C_{13}H_{14}N_2S$: S, 13.9%.
Found: S, 13.9%.

3'-Chloro-2,4-diaminodiphenyl Sulfide

Four g. (0.0129 mole) of the dinitro sulfide was reduced with hydrogen over Raney nickel. After two crystallizations of the isolated product from dilute ethanol, 2.5 g. (77.5%) of long, transparent needles melting at 94°-95° was obtained.

Anal. Calcd. for $C_{12}H_{11}N_2ClS$: S, 12.76%.
Found: S, 13.6%.

4'-Chloro-2,4-diaminodiphenyl Sulfide

Six g. (0.0193 mole) of the dinitro compound suspended in alcohol was catalytically reduced with hydrogen. After two crystallizations of the product from ethanol, 4.2 g. (87%) of flat, rectangular, colorless plates was secured melting at 141°-142°.

Anal. Calcd. for $C_{12}H_{11}N_2ClS$: S, 12.76%.
Found: S, 12.7%.

4'-Isopropyl-2,4-diaminodiphenyl Sulfide

Ten g. (0.0314 mole) of the pure dinitro sulfide was reduced to the amine with hydrogen over Raney nickel catalyst. From the filtered, concentrated, cooled, and water-diluted solution, shiny, light-brown blades of product melting at 93.5°-94° separated. Yield, 6.6 g (81.5%)

Anal. Calcd. for $C_{15}H_{18}N_2S$: S, 12.43%.
Found: S, 12.55%.

4-Aminodiphenyl Sulfone

Twenty g. (0.076 mole) of the nitro sulfone was reduced in the manner heretofore described, with tin and hydrochloric acid. A yield of 12 g. (68%) of faintly pinkish needles was obtained by crystallization from ethanol. Melting point, 174°-175°. (Reported:[181] 176°.)

3'-Methyl-4-aminodiphenyl Sulfone

Twenty g. (0.0722 mole) of the nitro compound was reduced with tin and hydrochloric acid. After three crystallizations of the crude product, extracted from the tin residues with ethanol, fine, pinkish needles melting at 184.5°-185.5° were obtained. Yield, 10.3 g. (58%).

Anal. Calcd. for $C_{13}H_{13}O_2NS$: S, 12.97%.
Found: S, 13.00%.

4'-Methyl-4-aminodiphenyl Sulfone

Twenty g. (0.0722 mole) of the precursor substance was reduced with tin and hydrochloric acid to yield, after three crystallizations from ethanol, 12 g. (68%) of product melting at 181°-182°. (Reported:[106] 181.5°, prepared by a different method.)

2'-Chloro-4-aminodiphenyl Sulfone

From 11 g. (0.037 mole) of the nitro compound reduced catalytically with hydrogen, a pink powder was obtained, which occurred as long, nearly colorless needles melting at 142°-144° after being twice recrystallized from dilute ethanol. Yield, 4.3 g. (43.5%).

Anal. Calcd. for $C_{12}H_{10}O_2NClS$: S, 11.97%.
Found: S, 11.82%.

3'-Chloro-4-aminodiphenyl Sulfone

The catalytic reduction with hydrogen of 11 g. (0.037 mole) of the nitro sulfone provided 7.5 g. (76%) of white needles melting at 189°-190° after three crystallizations of the product from dilute ethanol.

Anal. Calcd. for $C_{12}H_{10}O_2NClS$: S, 11.97%
Found: S, 11.96%.

4'-Chloro-4-aminodiphenyl Sulfone

Following the catalytic reduction of 4 g. (0.0135 mole) of the nitro sulfone in ethanol, long, white needles of the

rather insoluble amime were obtained. The melting point was in the range of 180°, but not sharp. After at least ten recrystallizations from ethanol, benzene, or glacial acetic acid, the melting point was constant and well-defined at 184°-185°. A mixed melting point with the precursor nitro compound, which melts at 182°-183°, (see ref. 182) was depressed 35°. Yield, 1.1 g. or 30.6%. (Reported:[185] 182°-183°.)

Anal. Calcd. for $C_{12}H_{10}O_2NClS$: N, 5.34%.
Found: N, 5.38%.

4'-Isopropyl-4-aminodiphenyl Sulfone

Eleven g. (0.0361 mole) of the nitro compound was reduced catalytically. From the reaction solution beautiful, nearly white crystals melting at 154.5°-155.5° separated out. Recrystallization did not raise the melting point. Yield, 8.5 g. or 86%.

Anal. Calcd. for $C_{15}H_{17}O_2NS$: S, 11.65%.
Found: S, 11.68%

3'-Methyl-2,4-diaminodiphenyl Sulfone

Twelve g. (0.0373 mole) of the nitro sulfone was reduced to the amine catalytically. After four crystallizations of the product from ethanol, a yield of 6.6 g. (67.5%) of pur-

---

185. Burton and Hoggarth (ref. 37) published an account of the preparation of this compound after the above work was completed.

plish-brown crystals melting at 153°-154° resulted.

Anal. Calcd. for $C_{13}H_{14}O_2N_2S$: S, 12.22%.
Found: S, 12.38%.

4'-Chloro-2,4-diaminodiphenyl Sulfone

Six g. (0.0175 mole) of the precursor compound, following catalytic reduction, gave transparent, purplish plates of amine melting at 200.5°-201.5° after three crystallizations from ethanol. The yield was 4 g. or 81%.

Anal. Calcd. for $C_{12}H_{11}O_2N_2ClS$: S, 11.32%.
Found: S, 11.52%.

Attempted Preparation of 3'-Chloro-2,4-diaminodiphenyl Sulfone

When 4.5 g. (0.01313 mole) of the dinitro sulfone was shaken with hydrogen and Raney nickel catalyst under 3 atm. pressure, the required amount of hydrogen for reduction of the two nitro groups was absorbed, but on working the product up, nothing but an unmanageable, dark, amorphous gum could be obtained.

Attempted Preparation of 4'-Isopropyl-2,4-diaminodiphenyl Sulfone

In catalytically reducing 8 g. (0.0228 mole) of the precursor nitro compound, the required amount of hydrogen for the reduction was absorbed; however, the product was an amorphous, brown solid, obviously quite impure. Many polyamines are easily oxidised on contact with the air. It seems

highly probable that by taking greater precautions to avoid contact with air, this aminosulfone and the one immediately preceding, could be prepared.

3'-Methyl-4-acetylaminodiphenyl Sulfide

Three g. (0.0139) of the 3'-methyl-4-aminodiphenyl sulfide was dissolved in 10 ml. of acetic anhydride and 15 ml. of glacial acetic acid, refluxed for one hour, and poured into an excess of water. The gummy residue was crystallized twice from dilute ethanol. Melting point, 121°-122°.

Anal. Calcd. for $C_{15}H_{15}ONS$: S, 12.47%.

Found: S, 12.40%.

3'-Methyl-4-formylaminodiphenyl Sulfide

Five g. (0.0232 mole) of the amine was refluxed five hours in 50 ml. of 87% formic acid, and then drowned in a large volume of cracked ice. The light, pink blades which separated out on standing were filtered off, dried, and twice recrystallized from dilute ethanol giving 3.7 g. (67%) of product melting at 72.5°-73.5°. The starting material itself melts at 72°-73°, but a mixed melting point of the two compounds was depressed to 50°-55°.

Anal. Calcd. for $C_{14}H_{13}ONS$: S, 13.2%.

Found: S, 13.5%.

3'-Methyl-4-ureidodiphenyl Sulfide

Five g. (0.023 mole) of 3'-methyl-4-aminodiphenyl sulfide was dissolved in 50 ml. of 50% ethanol containing 2.2 ml. (0.025 mole) of concentrated hydrochloric acid and refluxed for thirty minutes with 2.1 g. (0.026 mole) of potassium cyanate. During the course of the reaction 25 ml. of ethanol was added. The solution was filtered hot to remove a small amount of suspended solid, and cooled. The product showed a pronounced tendency to oil out. It was redissolved in ethanol, filtered, cooled, and filtered. After two recrystallizations from a mixture of 3 ml. of ethanol and 100 ml. of benzene, a pure, white powder was obtained melting at 150°-151° unchanged by further recrystallization. The yield was 2.5 g. (42%).

Anal. Calcd. for $C_{14}H_{14}ON_2S$: N, 10.84%.

Found: N, 10.87%.

p-(2,5-Dimethyl-1-pyrryl)phenyl m-Tolyl Sulfide

The 2,5-dimethyl-1-pyrryl derivatives of some of the foregoing amines were prepared essentially in accordance with the procedure (B) of Hazelwood, Hughes, and Lions.[186] The following procedure is illustrative of that used in the succeeding syntheses.

---

186. Hazelwood, Hughes, and Lions, J. Proc. Roy. Soc. N. S. Wales, 71, 92 (1937). /C. A., 32, 1695 (1938)/

In the presence of one ml. of glacial acetic acid as a catalyst, 6.45 g. (0.03 mole) of 3'-methyl-4-aminodiphenyl sulfide and 3.4 g. (0.03 mole) of 2,5-hexanedione (acetonylacetone) were condensed together in 15 ml. of absolute ethanol by refluxing for one and one-half hours. The solution was poured into 200 ml. of water; the solid product was filtered off, dried, and recrystallized from dilute ethanol. The yield was 6.5 g. (75%) of white crystals melting at 66°.

Anal. Calcd. for $C_{19}H_{19}NS$: N, 4.70%.
Found: N, 4.78%.

p-(2,5-Dimethyl-1-pyrryl)diphenyl Sulfide

Six g. (0.03 mole) of p-aminodiphenyl sulfide was condensed with 3.42 g. (0.03 mole) of acetonylacetone. After crystallization of the product from ethanol, 7 g. (84%) of white crystals melting at 86.5°-87° was obtained.

Anal. Calcd. for $C_{18}H_{17}NS$: N, 5.03%.
Found: N, 5.22%.

o-(2,5-Dimethyl-1-pyrryl)diphenyl Sulfide

From 3.5 g. (0.0174 mole) of the amine and 2 ml. of acetonylacetone, 2.9 g. (60%) of long, pinkish crystals melting at 116°-117° was obtained after two crystallizations from alcohol.

Anal. Calcd. for $C_{18}H_{17}NS$: N, 5.03%.
Found: N, 5.05%.

o-(2,5-Dimethyl-1-pyrryl)phenyl o-Tolyl Sulfide

Equimolar amounts (0.03 mole) of the amine and acetonylacetone were condensed, and the product was crystallized from alcohol as large, brown, cubical crystals melting at 108° unchanged by further crystallization. Yield, 6.9 g. (80%). For analysis a sample was dried in vacuo over phosphorus pentoxide at 80°.

Anal. Calcd. for $C_{19}H_{19}NS$: S, 10.94%.
Found: S, 11.08%.

o-(2,5-Dimethyl-1-pyrryl)phenyl p-Tolyl Sulfide

The condensation of 6.45 g. (0.03 mole) of the amine and 3.5 ml. (0.03 mole) of acetonylacetone provided a product from which 3.25 g. (37.4%) of white crystals melting at 78°-85° was obtained after two crystallizations from ethanol. Further recrystallization did not alter its rather ill-defined melting point.

Anal. Calcd. for $C_{19}H_{19}NS$: S, 10.94%.
Found: S, 10.96%.

p-(2,5-Dimethyl-1-pyrryl)phenyl o-Tolyl Sulfide

2'-Methyl-4-aminodiphenyl sulfide, 8.6 g. (0.04 mole), and 4.7 ml. (0.04 mole) of acetonylacetone were easily condensed to give large, white crystals of the product. It melted sharply at 111.5°-112° after two crystallizations from ethanol. Yield, 10 g. (85.5%).

Anal. Calcd. for $C_{19}H_{19}NS$: S, 10.94%.
Found: S, 11.14%.

p-(2,5-Dimethyl-1-pyrryl)diphenyl Sulfone

Seven g. (0.03 mole) of 4-aminodiphenyl sulfone was condensed with 3.42 g. (0.03 mole) of acetonylacetone for eight hours, rather than the usual one to three hours, giving 3.6 g. (39%) of beautiful, white plates. The melting point was 153°-154°.

Anal. Calcd. for $C_{18}H_{17}O_2NS$: N, 4.50%; S, 10.3%.
Found: N, 4.58%; S, 10.5%.

p-(2,5-Dimethyl-1-pyrryl)phenyl m-Tolyl Sulfone

From the condensation of 7.4 g. (0.03 mole) of the amine with an equivalent amount of acetonylacetone, 6.35 g. (65%) of pale tan crystals were isolated, melting at 121°-122° after several recrystallizations from ethanol and water.

Anal. Calcd. for $C_{19}H_{19}O_2NS$: N, 4.13%; S, 9.87%.
Found: N, 4.18%; S, 10.2%.

p-(2,5-Dimethyl-1-pyrryl)phenyl p-Tolyl Sulfone

The condensation of 7.4 g. (0.03 mole) of the amine and 3.42 g. (0.03 mole) of acetonylacetone yielded 8.2 g. (84%) of product recrystallized to a constant melting point of 148°-149°.

Anal. Calcd. for $C_{19}H_{19}NS$: S, 9.87%.
Found: S, 9.80%.

B. Quinoxaline Intermediates and Derivatives

1,2,4-Triaminobenzene

According to the general procedure of Hinsberg[187] for reducing 2,4-dinitroaniline with tin and hydrochloric acid, 91.5 g. (0.5 mole) of the nitroaniline, 250 g. (2.1 moles) of tin and 900 g. of concentrated hydrochloric acid in a 2 l. flask were warmed with frequent shaking in a water bath. The reaction began slowly, later becoming quite violent. When the reaction had subsided, the solution was filtered, evaporated to incipient crystal formation, and diluted with an equal volume of ethanol and concentrated hydrochloric acid (1:1). The black solid which deposited on cooling was taken up in a minimum of boiling water, diluted as before with ethanol and hydrochloric acid, and cooled. In this way 30 g. of beautiful green crystals of 1, 2, 4-triaminobenzene dihydrochloride was obtained. In the same way an additional 20 g. of product was recovered from the mother liquors. The total yield was 40 g. (41%).

In another run of 0.25 mole, using mechanical stirring to moderate the vigor of the reaction, which was processed as described above, a yield of 23 g. (71.5%) of the product was secured. Considerable by-product, the crystalline chlorostannic (or -ous) acid complex of the amine was obtained in these

187. Hinsberg, Ber., 19, 1253 (1886).

and subsequent runs, from which it was very difficult to isolate the amine hydrochloride.

Catalytic reduction method. In 300 ml. of absolute ethanol 61 g. (0.33 mole) of 2,4-dinitroaniline was suspended together with 4-5 g. of "wet" Raney nickel catalyst and shaken under 1-3 atm. of hydrogen until the required amount for complete reduction of the nitro groups had been absorbed (approx. 12 hours). The violet solution was filtered free of catalyst and treated with an excess of concentrated hydrochloric acid with cooling in an ice bath. A purple, fine, crystalline solid separated out, which was filtered off, washed with ethanol and ethyl acetate, and finally dried over anhydrous calcium chloride in vacuo. The yield of dry, purple solid was 52.5 g. (81%).

From five succeeding runs the yields obtained were 86%, 93%, 86%, 98%, and 85%, respectively.

2,3-Dimethyl-6-aminoquinoxaline

To 40 g. (0.204 mole) of 1,2,4-triaminobenzene dihydrochloride (obtained by catalytic reduction) dissolved in 200 ml. of water, 22 g. (0.216 mole) of diacetyl was slowly added with stirring. An exothermic reaction ensued, and a precipitate began to form. After digesting the mixture on the hot plate for some time, it was cooled and filtered. The precipitate was resuspended in water, made alkaline with sodium hydroxide

solution, cooled, filtered, and washed with water. The dry powder, melting at 186°-187°, was crystallized from benzene-ethanol (3:1) as long, brown needles melting at 186°-187°. In solution it exhibits a strong flouresecence, being red by transmitted light and yellowish-green by reflected light. The yield was 35 g., which is nearly quantitative.

In a smaller run (0.102 mole) using the amine obtained by catalytic reduction, the small excess of diacetyl was removed by steam distillation of the acidic suspension of the quinoxaline. Great difficulty was encountered in freeing the product of tar, which was finally removed by repeated treatment with Norit of the product dissolved in large amounts of hot water, followed by recrystallization from benzene-ethanol. The yield of product melting at 186°-187° was 10 g. (57%).

Anal. Calcd. for $C_{10}H_{11}N_3$: N, 24.2%.

Found: N, 23.9%.

2,3-Dimethyl-6-(2,5-dimethyl-1-pyrryl)quinoxaline

Three g. (0.017 mole) of 2,3-dimethyl-6-amino quinoxaline in 12 ml. of absolute ethanol was refluxed for four hours with 2.18 g. (0.0191 mole) of acetonylacetone and 1 ml. of glacial acetic acid as a catalyst. It was poured with rapid stirring into 50 ml. of water, cooled, and filtered. The granular product was crystallized from ethanol after treatment with Norit as long, straw-colored needles melting at 161°-163°. The yield was 3.2 g. or 74%.

Anal. Calcd. for $C_{16}H_{17}N_3$: N, 16.7%.
Found: N, 16.75%.

In another run of the same size, 2 g. (47%) of thin, golden leaflets melting at 162°-164° was obtained from alcoholic solution.

Attempted Preparation of 2-(2,5-dimethyl-1-pyrryl)quinoxaline

Alloxazine was prepared from 21.6 g. (0.2 mole) of o-phenylenediamine and 32 g. (0.2 mole) of alloxan hydrate according to the method of Kuhling.[123] The yield was 41.5 g. (97%). It decomposes above 300° without melting.

Following the method of Weijlard, Tishler, and Erickson,[142] 20 g. (0.0935 mole) of crude alloxazine was autoclaved at 175° for two hours with 100 ml. of 28% aqueous ammonia. The moist cake was boiled with 300 ml. of water to expel ammonia, charcoaled, and acidulated with hydrochloric acid to a pH of 2.5. On cooling, bright yellow crystals of 2-amino-3-carboxyquinoxaline were obtained. The yield was 13 g. (73.5%), melting with decomposition at 202°. The product was decarboxylated to 2-aminoquinoxaline in boiling nitrobenzene, poured into petroleum ether, washed, and dried. Yield, 91.5%.

From 3.5 g. (0.0242 mole) of 2-aminoquinoxaline refluxed for two hours in 15 ml. of absolute ethanol with 3 ml. of acetonylacetone and 1 ml. of glacial acetic acid, a dark, brown gum and 2 g. of crystalline material was isolated on drowning in water. The gum could not be purified. After

three crystallizations from ethanol-water (1:3) the crystalline product melted at 153°-154°. A portion of it melted at 156°-157° after sublimation. (Reported:[142] 155°-156° for 2-amino-quinoxaline.)

On a second attempt only a dark unmanageable gum was obtained.

Anisoin

Following the general procedure of Dewar and Read,[188] who state that cyanate-free cyanide and acid-free aldehyde are essential to success, 200 g. (1.47 mole) of anisaldehyde, freshly washed with 10% sodium carbonate, was refluxed for two hours with 300 ml. of ethanol, 160 ml. of water, and 40 g. of potassium cyanide (96% pure). Forty g. more potassium cyanide was then added, and the mixture was refluxed another two hours. On cooling and scratching the inner walls of the flask, the product was induced to crystallize. A yield of 86 g. (43%) of yellow crystals melting at 113° was obtained. (Dewar and Read claim yields as high as 75% after reworking the mother liquors.)

Another run gave a yield of 40%. A third run made according to the "Darstellung" procedure of Beilstein gave only a 22% yield.

---

188. Dewar and Read, J. Soc. Chem. Ind., 55T, 347T (1936).

Anisil

Eleven g. (0.0405 mole) of anisoin was added to a hot mixture of 45 g. (0.18 mole) of hydrated copper sulfate, 20 ml. of water, and 60 g. of pyridine in a 250 ml. three-necked flask and heated on a steam bath with stirring for four hours. Then the solution was slowly poured with stirring into 200 ml. of cold water. On filtering and washing copiously with water, fine, pale yellow crystals melting sharply at 131°-132° were obtained without crystallization. The yield was 10.5 g. (96%). (Reported:[189] 133°, by another technique.)

Two more runs made in the same manner gave yields of 96% and 100%.

6-Amino-2,3-bis(p-methoxyphenyl)quinoxaline

Ten g. (0.037 mole) of anisil and 7.5 g. (0.038 mole) of 1,2,4-triaminobenzene dihydrochloride dissolved in 100 ml. of ethanol and water (1:1) were refluxed with stirring on a steam bath for four hours. A slight excess of concentrated sodium hydroxide solution was added, and the mixture cooled. The hard cake of crude product from the reaction was ground in a mortar, dissolved in hot ethanol, charcoaled, and cooled. Dark, purplish, shining crystals separated out. Recrystallization from benzene, which seemed to be a more suitable solvent, gave 8.1 g. (61.5%) of light brown crystals melting

189. Boesler, Ber., 14, 327 (1881).

at 194°-196° unchanged by further crystallization.

This compound exhibits a strong, deep green fluorescence even in extremely dilute solutions.

Another run (0.111 mole) gave 33.5 g. (59.5%) of pure product melting at 194°-196°.

Anal. Calcd. for $C_{22}H_{19}O_2N_3$: N, 11.76%.
Found: N, 11.71%.

6-(2,5-Dimethyl-1-pyrryl)-2,3-bis(p-methoxyphenyl)quinoxaline

Five g. (0.014 mole) of 2,3-bis(p-methoxyphenyl)-6-amino-quinoxaline, 2.5 ml. of acetonylacetone, and 1 ml. of glacial acetic acid catalyst in 40 ml. of ethanol were refluxed together for four hours. On cooling, a mass of golden platelets and some black tar deposited from the solution. It melted at 194°-198°. The product was suspended in 30 ml. of ethanol and refluxed while benzene was added dropwise until complete solution of the solid was just effected. The solution was treated with Norit, filtered, and cooled to crystallization. After a repetition of this purification procedure, 3.6 g. (59%) of deep yellow crystals melting at 189°-190° was obtained.

Anal. Calcd. for $C_{18}H_{15}O_2N_3$: N, 9.65%.
Found: N, 9.70%.

6-Amino-2,3-diphenylquinoxaline

Twenty g. (0.095 mole) of benzil and 18.5 g. (0.095 mole) of 1,2,4-triaminobenzene dihydrochloride were refluxed together

with stirring in 150 ml. of ethanol and water (1:1) on a steam bath for one hour. An excess of sodium hydroxide solution was slowly dropped in, and the mixture was cooled. The crude product was taken up in hot ethanol charcoaled, filtered, and evaporated to dryness. After crystallization from benzene, yellow crystals melting at 172°-173° were obtained. The yield was 16 g. (57%). (Reported:[122] 175°.)

6-(2,5-Dimethyl-1-pyrryl)-2,3-diphenylquinoxaline

2,3-Diphenyl-6-aminoquinoxaline, 7 g. (0.0235 mole), was dissolved in as little boiling absolute ethanol as would conveniently dissolve it (45 ml.); then 3 ml. of acetonylacetone and 1 ml. of glacial acetic acid were added, and the mixture refluxed for five hours. When it was poured into water, only a colloidal emulsion resulted; however, the addition of a little sodium hydroxide to neutralize the acetic acid caused a deep yellow precipitate to form, which was filtered off and dried. Melting point, 100°-120°. The crude material was suspended in boiling ethanol, and benzene was slowly added until it had completely dissolved. On cooling, beautiful yellow crystals formed, melting at 148°-150°. A final recrystallization from benzene and ethanol gave 3.8 g. (43.5%) of large, yellow crystals melting at 151°-153°.

Anal. Calcd. for $C_{26}H_{21}N_3$: N, 11.2%.

Found: N, 11.12%.

2,2'-Dichlorobenzil

2,2'-Dichlorobenzoin was prepared from 100 g. (0.712 mole) of o-chlorobenzaldehyde according to the procedure of Hodgson and Rosenberg;[190] however, the product was an oil which did not crystallize on cooling nor on treatment with solvents. (Reported:[190] 56°-57°, in 40% yield.)

The crude mixture obtained from the above reaction was added to a hot solution of 180 g. of hydrated copper sulfate in 80 ml. of water and 240 ml. of pyridine, and stirred on a steam bath for four hours. Almost immediately yellow crystals began to separate from the mixture. The mixture was drowned in 500 ml. of water, which precipitated a matrix of brown crystals and gum. On acidifying the filtrate with hydrochloric acid, a yellow precipitate was obtained, which was entirely organic, burning without residue, yet was insoluble in water, alkali, ethanol, or benzene. The crude, brown, crystalline material was crystallized from benzene as beautiful yellow needles melting at 128°-129°. (Reported:[190] 128° by another method.) The overall yield was 38.5 g. or 39%.

6-Amino-2,3-bis(o-chlorophenyl)quinoxaline

For four hours 10 g. (0.0358 mole) of 2,2'-dichlorobenzil and 7.5 g. (0.038 mole) of 1,2,4-triaminobenzene dihydrochloride were refluxed with vigorous stirring in 250 ml. of 60% ethanol in water. The sparingly soluble benzil went completely

190. Hodgson and Rosenberg, J. Chem. Soc., 16 (1930).

into solution. The mixture was alkalinized with sodium hydroxide and poured into water. The gummy precipitate solidified to a hard glass on cooling. It was taken up in hot benzene, charcoaled, filtered, and diluted with ligroin. The crystals separating out on cooling melted at 174°-177°. After being twice more recrystallized from benzene and ligroin, 7.25 g. (55%) of golden-brown platelets melting at 178°-179°, unchanged by further recrystallization, was obtained.

On another run using 20 g. (0.0716 mole) of the benzil, 14 g. (53.5%) of the pure product melting at 178°-179° was obtained.

Anal. Calcd. for $C_{20}H_{13}N_3Cl_2$: N, 11.47%.
Found: N, 11.48%.

6-(2,5-Dimethyl-1-pyrryl)-2,3-bis(o-chlorophenyl)quinoxaline

Seven g. (0.0191 mole) of 6-amino-2,3-bis(o-chlorophenyl)-quinoxaline was dissolved in 35 ml. of boiling absolute ethanol. After adding 2.5 ml. of acetonylacetone and 1 ml. of glacial acetic acid, refluxing for four hours, and drowning in 200 ml. of water containing a little sodium hydroxide, a gum changing to a friable yellow solid was obtained. This was dissolved in benzene, charcoaled, diluted with ligroin, cooled, and filtered. After two such crystallizations a yellow solid melting ca. 170° resulted. Then it was recrystallized three times from ethanol containing just enough benzene to effect complete solution, with intervening treatment with Norit.

Finally, 2.5 g. (39.4%) of pure, yellow crystals was secured, melting at 211°-212° unchanged by further crystallization.

Anal. Calcd. for $C_{26}H_{19}N_3Cl_2$: N, 9.46%.
Found: N, 9.67%.

2,3-Bis(p-nitrophenyl)quinoxaline

4,4'-Dinitrobenzil was prepared after the method of Chattaway and Coulson[191] by the nitration of 4,5-diphenylglyoxalone.

From 100 g. (0.472 mole) of pure benzoin and 52 g. (0.868 mole) of urea, a yield of 90 g. (81%) of 4,5-diphenylglyoxalone was obtained.

The semi-solid mass obtained following the nitration of 4,5-diphenylglyoxalone was fractionally recrystallized five times from hot glacial acetic acid until the melting point of the yellow, crystalline 4,4'-dinitrobenzil had been raised to 206°-209°. (Reported:[191] 213°.)

Two g. (0.0066 mole) of the benzil and 0.7 g. (0.0066 mole) of o-phenylenediamine were refluxed in 50 ml. of glacial acetic acid for two hours. Then the solution was concentrated to 15 ml. and allowed to cool. Large, well-formed, tan crystals of product were obtained on filtering, washing, and drying. The yield was 2.45 g. (100%). Melting point, 203°-204°. (Reported:[191] 201°.)

---

191. Chattaway and Coulson, J. Chem. Soc., 1361 (1928).

2,3-Bis(p-aminophenyl)quinoxaline

2,3-Bis(p-nitrophenyl)quinoxaline, 2.3 g. (0.0062 mole), was suspended in 60 ml. of absolute ethanol together with 1-2 g. of Raney nickel and shaken under 3 atm. pressure of hydrogen until the required amount of hydrogen was absorbed. The insoluble deposit was dissolved in methyl cellosolve, and the solution filtered free of catalyst. On evaporation of most of the solvent and diluting with water, brownish-yellow crystals melting at 255°-258° were obtained. The product was recrystallized successively from acetone and water, and then from acetone and ethanol until the melting point was constant at 260°-262°. The yield of shining, yellow plates was 0.350 g. or 18% yield after all the losses of recrystallizations.

Kuhn and co-workers[192] have prepared this compound by a different method. They give its melting point as 267°-268°.

Anal. Calcd. for $C_{20}H_{16}N_4$: N, 17.94%.

Found: N, 17.95%.

4,4'-Dihydroxybenzil

Schönberg and Kraemer[193] describe the preparation of this compound from anisil using hydrobromic acid of 1.78 density. Since fuming hydrobromic acid of that quality was not available, adaptations using available materials were tried.

---

192. Kuhn, Möller, and Wendt, Ber., 76, 412 (1943).

193. Schönberg and Kraemer, Ber., 55, 1188 (1922).

Eight g. of anisil was dissolved in just enough hot glacial acetic acid to effect solution; then constant boiling hydrobromic acid (d. 1.48) was added until the appearance of a faint turbidity. The mixture was refluxed for five hours and poured into water. The precipitated gum was extracted with a large volume of cold, concentrated sodium hydroxide solution and filtered. All but a little residue dissolved. On acidifying and cooling the filtrate, a product was obtained melting over a wide range beginning below 100°. Obviously the demethylation was incomplete.

Next, 8 g. of anisil was refluxed for several hours with a very large excess of 33% hydrogen bromide in glacial acetic acid for twenty-four hours. After working the reaction mixture up in the same manner as outlined above, the demethylation was found to be very incomplete.

Finally, 10 g. (0.037 mole) of anisil, 50 ml. of aqueous hydrobromic acid (d. 1.48), and 50 ml. of 33% hydrogen bromide in glacial acetic acid were refluxed with vigorous stirring for six hours, and then poured into water. A fine, gray powder separated, which easily dissolved in a small volume of 15% sodium hydroxide leaving no insoluble residue. Precipitation with hydrochloric acid gave a light gray powder melting at 245°-247°. A portion crystallized from a large volume of boiling water likewise melted at 245°-247°. The yield was 8 g. (89.4%). (Reported:[193] 235°.)

2,3-Bis(p-hydroxyphenyl)quinoxaline

In 75 ml. of glacial acetic acid, 1.1 g. (0.01 mole) of o-phenylenediamine and 2.4 g. (0.01 mole) of 4,4'-dihydroxybenzil were refluxed for three hours. On cooling, 2,3-bis-(p-hydroxyphenyl)quinoxaline crystallized out as glistening, brown crystals. It is easily soluble in sodium hydroxide but very difficultly soluble in hydrochloric acid.

The yield was 2.9 g. (94%) of product melting at 321°-323°. After crystallization from ethanol as yellow crystals, the melting point was 326°-328°.

Anal. Calcd. for $C_{20}H_{14}O_2N_2$: N, 8.91%
Found: N, 9.02%.

6-Amino-2,3-bis(p-hydroxyphenyl)quinoxaline

In 25 ml. of 50% ethanol in water, 2.4 g. (0.01 mole) of 4,4'-dihydroxybenzil and 1.96 g. (0.01 mole) of 1,2,4-triamino-benzene dihydrochloride were stirred and refluxed for two hours. Then the pH of the mixture was adjusted to the isoelectric point with sodium hydroxide and hydrochloric acid. The amorphous, brown precipitate was boiled in ethanol and water with Norit, filtered, and cooled. Tiny, iridescent, orange needles crystallized out, melting at 338°-340°. The compound dissolves in acids giving a cherry red solution and in bases giving a brilliant yellow solution. Since the change is reversible, it is an acid-base indicator. On testing a dilute solution of the compound in a series of standard Clark and Lubs buffers,

the change from red to yellow was found to occur between a pH of 3.4 and 3.6.

Anal. Calcd. for $C_{20}H_{15}O_2N_2$: N, 12.77%.
Found: N, 12.84%.

C. 2-Thiouracil Intermediates and Derivatives

1-Diethylamino-4-carbethoxyhexanone-5

Sodium ethoxide was prepared by dissolving 4.6 g. (0.2 atom) of clean sodium in 80 ml. of absolute ethanol in a 500 ml. three necked flask. Acetoacetic ester, 28.6 g. (0.22 mole), was added, and the mixture was gently refluxed while 30 g. (0.2 mole) of γ-diethylaminopropyl chloride was added dropwise over a two hour period. After a short while the solution became cloudy. It was refluxed for six hours, cooled, and filtered free of 10.6 g. of sodium chloride (11.6 g. theoretical).

After the bulk of the ethanol was distilled from the filtrate, the residue was poured into water and extracted with ether. The ether extract was dried over anhydrous sodium sulfate, filtered, and flashed into a 125 ml. Claisen flask modified by the insertion of a ten inch Vigreaux column. On distillation, an 8.6 g. forerun was collected at 41°-115°/0.6-0.9 mm. The principal fraction amounted to 23 g. distilling at 116°-139°/1 mm. The residue was small, about 5 g. From the aqueous layer considerable polymeric gum, likely arising from

quaternization of the γ-diethylaminopropyl chloride, was obtained on evaporation.

The main fraction was redistilled. After taking a small forerun at 93°-97°, the main fraction was collected at 98°-112° (largely 107°-109°)/0.5 mm. weighing 17.8 g. (36.5%).

N_D^{20} 1.4514; D_4^{20} 0.9559; M_D^{20} calcd. 69.06 (keto), 70.10 (enol); M_D^{20} obs. 69.0.

On another run of 0.35 mole using freshly distilled γ-diethylaminopropyl chloride boiling at 63°-66°/15 mm., about 60% of it was added all at once to the refluxing sodio acetoacetic ester solution. After two hours the remainder was added. After twenty hours of refluxing, the mixture was worked up as before. The residue on distillation gave a 7 g. forerun at 36°-99°/0.4 mm., and 53.6 g. (63%) of clear, colorless product boiling at 100°-107° (largely 104°-105°)/0.4 mm.

N_D^{20} 1.4509.

About 5 g. of viscous resin remained in the flask.

Anal. Calcd. for $C_{13}H_{26}O_3N$: N, 5.73%.
Found: 5.57% (Kjeldahl).

Attempted Preparation of 5-(γ-Diethylaminopropyl)-6-methyl-2-thiouracil

To 2.3 g. (0.10 atom) of sodium dissolved in 50 ml. of absolute ethanol, 5.33 g. (0.07 mole) of thiourea and 12.2 g. (0.05 mole) of 1-diethylamino-4-carbethoxyhexanone-5 were

added, and the solution was refluxed for fourteen hours on the steam bath. The solution became cloudy but no precipitate formed. After the excess solvent was removed in vacuo at 50°-60°, the residue was taken up in 50 ml. of water, filtered, and carefully acidified first with 7 ml. of concentrated hydrochloric acid and then with acetic acid. No matter how the pH was adjusted, no precipitate formed. The odor of hydrogen sulfide was detected in the mixture. After the solution was evaporated to dryness in vacuo over sulfuric acid, the gummy solid obtained was treated with various solvents. In this way the sodium chloride and sodium acetate were separated, but no pure organic component could be isolated either by attempted distillation or crystallization.

1-(γ-Diethylaminopropylmercapto)-3-carbethoxypentanone-4

γ-Diethylaminopropyl β-chloroethyl sulfide was prepared according to the directions of Gilman and Tolman.[194] From the sodium salt of 91 g. (1.17 moles) of β-hydroxyethyl mercaptan and 174.5 g. (1.17 moles) of γ-diethylaminopropyl chloride in 600 ml. of absolute ethanol was obtained 191.5 g. (86%) of γ-diethylaminopropyl β-hydroxyethyl sulfide boiling at 105°/0.1 mm. The constants, which have not heretofore been determined, are as follows:

N_D^{20} 1.4957; d_4^{20} 0.9830; M_D calcd. 57.3, found, 56.8.

---

194. Gilman and Tolman, J. Am. Chem. Soc., 67, 1847 (1945).

The β-hydroxyethyl sulfide was converted to the β-chloro derivative by treating 85 g. (0.445 mole) of it with 107 g. (0.9 mole) of thionyl chloride in 200 ml. chloroform at 0°. On distillation, 53.5 g. (57%) of product was obtained boiling at 84°-95°/0.3-0.4 mm. (bath 112°-132°). (The boiling point fluctuated with the bath temperature.) The constants, which have not been determined heretofore, are as follows:

N_D^{20} 1.4890; d_4^{20} 1.00015; M_D^{20} calcd. 60.7, found, 60.5.

It was stored in the form of its hydrochloride, as precipitated from anhydrous ether solution with dry hydrogen chloride. Just before use the free base was liberated with 10% sodium hydroxide, extracted with ether, and distilled.

The freshly distilled γ-diethylaminopropyl β-chloroethyl sulfide, 22.6 g. (0.108 mole), was added dropwise with stirring over a five hour period to the refluxed solution of sodio acetoacetic ester prepared from 15.6 g. (0.12 mole) of ethyl acetoacetate in 70 ml. of absolute ethanol. The sodium chloride (equivalent to theoretical) was filtered off, and the filtrate was evaporated to a small volume, cooled, poured into water, and extracted with ether. The residue from the dried, filtered, and evaporated extract was distilled through an eight inch Vigreaux column. Under 0.4 mm. pressure the following fractions were collected: a small amount at 58°-114°, 4.2 g. at 114°-149°, and 15 g. at 141°-157°.

The last fraction was redistilled at 0.4 mm. pressure giving 2-3 g. at 97°-120°, 2-3 g. at 125°-142°, and the principal fraction at 147°-150° weighing 11 g. (33.5%).

N_D^{20} 1.4811; d_4^{20} 1.0049; M_D^{20} calcd. 85.2 (keto), 86.3 (enol), found, 86.0.

Anal. Calcd. for $C_{15}H_{29}O_3NS$: S, 10.6%.
Found: S, 10.8%.

Attempted Preparation of 5-(γ-Diethylaminopropylmercaptoethyl)-6-methyl-2-thiouracil

To 1.52 g. (0.066 atom) of sodium dissolved in 33 ml. of absolute ethanol, 3.5 g. (0.046 mole) of thiourea, and 10 g. (0.033 mole) of 1-(γ-diethylaminopropylmercapto)-3-carbethoxy-pentanone-4 were added, and the mixture was refluxed for forty hours. No precipitate formed on heating. The excess solvent was evaporated at 50°-60° under the aspirator; the residue was taken up in 50 ml. of water, and carefully acidified with 4.5 ml. of concentrated hydrochloric acid and then with acetic acid until just acid to litmus. The solution was evaporated to dryness *in vacuo* at room temperature over concentrated sulfuric acid, but only an intractable brown gum completely unamenable to crystallization was obtained. Attempts to distill it, after being extracted from the inorganic salts with alcohol, were likewise fruitless. Decomposition occurred on heating.

6-Methyl-2-thiouracil

According to the general method of Wheeler and McFarland[152] from 9.2 g. (0.4 atom) of sodium, 21.3 g. (0.28 mole) of thiourea, and 26 g. (0.2 mole) of acetoacetic ester dissolved in 200 ml. of absolute ethanol, a voluminous precipitate was obtained on refluxing for six hours. After removing the solvent under reduced pressure, taking the residue up in 150 ml. of water, and precipitating the product with 28 ml. of hydrochloric acid and with acetic acid, a pure, white powder was obtained decomposing above 300°. The yield was 27.5 g. (97%). On another run the yield was 84%.

Attempted Preparation of 2-(p-Nitrophenylmercapto)-4-hydroxy-6-methylpyrimidine

To 1.15 g. (0.05 atom) of sodium dissolved in 50 ml. of absolute ethanol was added 7.1 g. (0.05 mole) of 6-methyl-2-thiouracil, forming a suspension of the sodium salt of the uracil. Then 7.9 g. (0.05 mole) of p-nitrochlorobenzene in 25 ml. of ethanol was added, and the mixture was stirred and refluxed for eight hours. Then the mixture was filtered. From the ethanol-washed precipitate the 6-methyl-2-thiouracil was recovered unchanged, while from the filtrate the p-nitrochlorobenzene was recovered. There was no evidence of reaction having taken place.

Attempted Preparation of 2-(o-Nitrophenylmercapto)-4-hydroxy-6-methylpyrimidine

The experiment immediately preceding was repeated using the same quantities of material and procedure, but substituting o-nitrobromobenzene for the p-nitrochlorobenzene used above. Again both the 6-methyl-2-thiouracil and the halonitrobenzene were recovered unchanged following eight hours of refluxing.

Attempted Preparation of 2-(2,4-Dinitrodiphenylmercapto)-4-hydroxy-6-methylpyrimidine

A suspension of the sodium salt of 6-methyl-2-thiouracil (0.05 mole) was prepared in 75 ml. of absolute ethanol. To this, 10.1 g. (0.05 mole) of 2,4-dinitrochlorobenzene was added, and the mixture was stirred and refluxed for six hours. The yellow precipitate, which had formed, was filtered, washed well with water to remove the soluble salts, and dried. The resulting solid, which was extremely insoluble in most solvents was first crystallized in micro-crystalline form from 700 ml. of methyl cellosolve and then from 1 l. of glacial acetic acid. The product melted with decomposition at ca. 248°-250°.

Anal. Calcd. for $C_{11}H_9O_5N_4S$: N, 18.1%; S, 10.38%.
Found: N, 17.2%; S, 13.08%.

Further attempts at purification seemed to have little effect.

2-(γ-Diethylaminopropylmercapto)-4-hydroxy-6-methylpyrimidine

A suspension of the sodium salt of 6-methyl-2-thiouracil was prepared by digesting 7.1 g. (0.05 mole) of the uracil in a solution of 1.15 g. (0.05 atom) of sodium in 50 ml. of absolute ethanol at reflux temperatures for two hours. Then 7.5 g. (0.05 mole) of γ-diethylaminopropyl chloride in 25 ml. of ethanol was added, and the mixture was stirred and refluxed for six hours. The cooled mixture was filtered free of sodium chloride, and the filtrate evaporated. The residue was distilled at 183°-188°/0.4 mm. with no forerun, giving 10.5 g. (82.4%) of a colorless, very viscous oil, almost a glass. It was very soluble in ethanol, insoluble in water and ligroin, and sparingly soluble in ether.

Anal. Calcd. for $C_{12}H_{21}ON_3S$: N, 16.47%.
Found: N, 16.65%.

Ethyl Picolinoylacetate

This ester was prepared according to the method of Gilman, Tolman, and Massie,[195] who did not, however, isolate the product, but hydrolyzed it directly to the ketone *in situ*. The isolation of the free base has not been heretofore reported in the chemical literature.

To 13.8 g. (0.6 atom) of sodium sand (sodium sand can be very conveniently prepared by using the efficient Hershberg

---

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

stirrer) suspended in 550 ml. of dry benzene, 27.6 g. (0.6 mole) of absolute ethanol was added dropwise at such a rate as to promote gentle reflux until all the sodium had disappeared (two hours). Then a mixture of 60.4 g. (0.4 mole) of ethyl picolinate[196] and 70.4 g. (0.8 mole) of ethyl acetate (dried over phosphorous pentoxide) was slowly run into the refluxing suspension. After the addition was complete, the reaction mixture set up to a thick sludge which could not be stirred. The precipitate was filtered off, dissolved in water, and treated with an excess of acetic acid to liberate the ester. After extraction with ether, drying, filtering, and evaporating, the residue was distilled. A red liquid distilling at 115°-120°/0.4 mm. weighing 24.4 g. and another fraction at 122°-124°/0.5 mm. weighing 29.9 g. were collected. On standing both liquids became a straw-yellow color. Their reactions indicated that both fractions were nearly pure ethyl picolinoylacetate. Yield, 54.3 g. (76%).

The identity of the product was established by refluxing a 0.01 mole portion with 0.01 mole of phenylhydrazine in 10 ml. of ethanol containing a few drops of acetic acid as a catalyst. On cooling, yellow needles of 1-phenyl-3-(α-pyridyl)pyrazolone-5 melting at 177°-178° were obtained. (Reported:[197] 179°.) Yield, 2 g. (85%).

---

196. This ester was kindly supplied by S. P. Massie of these laboratories.

197. Pinner, Ber., 34, 4237 (1901).

6-(α-Pyridyl)-2-thiouracil

Thiourea, 3.8 g. (0.05 mole), and 8.95 g. (0.05 mole) of ethyl picolinoylacetate were added to a solution of 2.3 g. (0.1 atom) of sodium in 50 ml. of ethanol. Almost immediately a precipitate began to form. After refluxing overnight the solvent was removed from the precipitate under reduced pressure, and the cake was dissolved in 50 ml. of water and filtered. The filtrate was first acidified with 4.4 ml. (0.05 mole) of concentrated hydrochloric acid and then with acetic acid until no further precipitation occurred. The precipitate was filtered off, dried, and crystallized from about 200 ml. of glacial acetic acid. Three g. (29%) of hard, well-formed crystals with a greenish cast were obtained. They melted with decomposition at 291°-294°. The product is readily soluble in both acids and bases.

Anal. Calcd. for $C_9H_7ON_3S$: N, 20.47%.

Found: N, 20.70%.

Ethyl Nicotinate

According to the general technique of Camps,[198] 100 g. (0.813 mole) of nicotinic acid was esterified by warming on a steam bath with a mixture of 250 ml. of absolute ethanol and 125 ml. of concentrated sulfuric acid (prepared with strong cooling of the components) until all the solid went into

198. Camps, Arch. Pharm., 240, 346 (1902).

solution. After cooling to 0°, the mixture was poured with vigorous stirring slowly into 2 kg. of cracked ice and 355 g. of potassium carbonate. The precipitate separating on standing was filtered off, and the filtrate was treated with 300 ml. of saturated sodium carbonate solution to salt out the ester. The ester was extracted with 2 l. of ether, dried, filtered, and flashed into a modified Claisen flask. With no forerun and virtually no residue the entire contents of the flask distilled at 107°-108°/16 mm. giving 88 g. (72%) of clear, colorless, brilliant liquid.

Ethyl Nicotinoylacetate

A suspension of 0.75 mole of sodium ethoxide in 690 ml. of anhydrous benzene was prepared from 17.25 g. (0.75 atom) of sodium sand and 34.6 g. (0.75 mole) of absolute ethanol. To this, a mixture of 88 g. (1.0 mole) of anhydrous ethyl acetate and 75.5 g. (0.5 mole) of ethyl nicotinate was added slowly, and the reaction mixture was stirred and refluxed for twelve hours. By this time the liquid became clear. The benzene was distilled on a steam bath, and the residual gum was hydrolyzed with a dilute solution of 60 ml. of glacial acetic acid in water. Then an excess of potassium carbonate was added, and the ester was extracted with ether. After drying, filtering, and evaporating the ether, the extract was distilled. A 24.9 g. forerun was collected at 56°-115°/0.4 mm., then the principal fraction was obtained at 121°-123°/0.4 mm. as a

pale, straw-colored oil weighing 64.5 g. (72%). (Reported, by another modification of the Claisen condensation: 37%,[199] as the hydrochloride, and 58%.[200]

6-(β-Pyridyl)-2-thiouracil

Thiourea, 5.3 g. (0.07 mole), and ethyl nicotinoylacetate, 8.95 g. (0.05 mole), were refluxed together for twelve hours in a solution of 2.3 g. (0.1 atom) of sodium in 50 ml. of ethanol, by which time a copious, white precipitate had formed. After removing the ethanol at 40°-70° under reduced pressure, the residue was taken up in 50 ml. of water, filtered, and acidified with 4.4 ml. (0.05 mole) of concentrated hydrochloric acid and then with acetic acid until a slight excess was present. The white precipitate was filtered off, dried, and recrystallized from glacial acetic acid as fine, white crystals melting with decomposition at 296°-298° unchanged by further crystallization. The yield was 3.9 g. (38%).

Anal. Calcd. for $C_9H_7ON_3S$: N, 20.47%.
Found: N, 20.42%.

Ethyl Isonicotinate

Isonicotinic acid was prepared by oxidising 200 g. (2.15 mole of γ-picoline (technical grade) in 3 l. of water with a

---

199. Burrus and Powell, J. Am. Chem. Soc., 67, 1468 (1945).
200. Bloom, Breslow, and Hauser, ibid., 67, 2207 (1945).

total of 680 g. (4.30 moles) of potassium permanganate added in three portions (the reaction tends to become violent). A yield of 155 g. (58.7%) of pure acid was obtained from the concentrated and carefully acidified filtrate.

One hundred and forty g. (1.14 mole) of isonicotinic acid suspended in 980 ml. of absolute ethanol was cooled to 0° while anhydrous hydrogen chloride was bubbled in with stirring until the mixture was saturated (two to three hours). Then with hydrogen chloride still being slowly passed in, it was refluxed until all the solid dissolved. The excess ethanol was removed under reduced pressure, and the solid cake dissolved in water, cooled in ice, and treated with an excess of saturated sodium carbonate solution. After filtering, the ester was extracted with ether. On evaporation of the ether, the residue was distilled giving 105.5 g. (61.4%), with no forerun, of clear, colorless ester boiling at 105°-108°/16-17 mm. (Reported:[199] 30% yield by the method of Camps.)

Ethyl Isonicotinoylacetate

A suspension of 0.75 mole of anhydrous, alcohol-free sodium ethoxide was prepared in 690 ml. of benzene from equimolar amounts of absolute ethanol and sodium sand.

A mixture of 88 g. (1.0 mole) of anhydrous ethyl acetate and 75.5 g. (0.5 mole) of ethyl isonicotinate was slowly run into the stirred and refluxing suspension of sodium ethoxide. The heating was continued overnight. A mobile, yellow suspen-

sion resulted. After removing the benzene on a steam bath, the residue was taken up in 60 ml. of glacial acetic acid in several hundred ml. of water and then shaken with an excess of potassium carbonate. The ester was extracted with ether, dried, filtered, and distilled. In a solids receiver, 66.4 g. (74.2%) of product boiling at 118°-120°/0.4-0.5 mm. was collected. It solidified to hard, white crystals, which were crystallized from 50% ethanol melting at 53°-55°. (Reported:[200] 54°, in 85% yield, by a different technique.)

6-(γ-Pyridyl)-2-thiouracil

To 4.6 g. (0.2 atom) of sodium in 100 ml. of absolute ethanol, 10.6 g. (0.14 mole) of thiourea and 17.9 g. (0.1 mole) of ethyl isonicotinoylacetate were added. After refluxing for twelve hours, the solvent was removed under reduced pressure from the precipitate, which was taken up in 100 ml. of water, filtered, and acidified with 9 ml. of concentrated hydrochloric acid and then with acetic acid in slight excess. Since the filtered and dried product was either insoluble or only slightly soluble in glacial acetic acid, nitrobenzene, carbitol, aniline, pyridine, quinaldine, tri-n-butyl phosphate and all common solvents, it was purified by dissolving it in alkali, filtering, reprecipitating with acetic acid, and washing with water. The compound decomposes ca. 355°-358°. Yield, 10.2 g. (49.7%).

Anal. Calcd. for $C_9H_7ON_3S$: S, 15.63%.
Found: S, 15.73%.

Ethyl p-Anisoylacetate

Sodamide was prepared by dissolving 9.2 g. (0.4 atom) of sodium in 250 ml. of liquid ammonia containing a small amount (ca. 1 g.) of anhydrous ferric chloride. When the sodium had all reacted, as evidenced by disappearance of the blue color and subsidence of the gray suspension of sodamide, 30 g. (0.2 mole) of p-methoxyacetophenone dissolved in 100 ml. of dry ether was added employing vigorous stirring. The excess ammonia was removed on the steam bath, replacing it with ether as it evaporated. When the ether started to reflux, 47.2 g. (0.4 mole) of pure ethyl carbonate was added. The suspension turned almost immediately from black to a light gray color. After stirring and refluxing for five hours, a semi-solid mass resulted, which was removed and hydrolyzed with 30 ml. of glacial acetic acid in 500 g. of ice. The ether layer was removed and the aqueous layer extracted with more ether. After drying the combined extracts over anhydrous potassium carbonate, the ether was evaporated, and the residue was distilled with considerable decomposition giving 11.9 g. (26.8%) of clear, viscous, straw-colored oil at 155°-158°/0.6-0.7 mm. (Reported:[201] boiling point 180°-190°/10-12 mm. with decomposition, prepared by another method.)

---

201. Wahl and Silberzweig, Bull. soc. chim. [4] 11, 27 (1912).

Since the preparation of this ester by the above method has not been heretofore reported, its identity was established by refluxing 0.5 g. each of the ester and hydroxylamine hydrochloride in ethanol. Long, slender, white needles of 3-(p-methoxyphenyl)isoxazolone-5 were obtained melting at 140°-141° after one crystallization from ethanol. (Reported:[202] 143°.)

6-(p-Methoxyphenyl)-2-thiouracil

In the presence of 0.1 mole of sodium dissolved in 50 ml. of absolute ethanol, 5.3 g. (0.07 mole) of thiourea and 10.5 g. (0.0473 mole) of ethyl p-anisoylacetate were condensed by refluxing for twelve hours. A white precipitate formed after several hours. The solvent was removed under reduced pressure, and the residue was dissolved in 50 ml. of water and filtered. On acidifying the filtrate with 4.4 ml. (0.05 mole) of concentrated hydrochloric acid and then with acetic acid in slight excess, a precipitate formed, which was filtered off, dried and crystallized from glacial acetic acid to a constant melting point. Compact, greenish crystals, 3.4 g. (31%), were obtained softening at 285° and melting with decomposition at 288°-289°.

Anal. Calcd. for $C_{11}H_{10}O_2N_2S$: N, 11.94%.
Found: N, 12.10%.

---

202. Wahl, Compt. rend., 148, 353 (1909).

Ethyl β-(2-thienyl)-β-oxopropionate

2-Acetothienone was prepared from commercial thiophene (Socony-Vacuum Oil Company) and freshly distilled acetyl chloride using stannic chloride as the condensing agent according to the method of Stadnikoff and Goldfarb.[203] The yield was 76.4%.

According to the general procedure of Levine and Hauser[204] 2-acetothienone was carbethoxylated in the presence of sodamide. To 0.4 mole of sodamide in 250 ml. of liquid ammonia, 25.25 g. (0.2 mole) of 2-acetothienone in 100 ml. of dry ether was added. After removing the ammonia on the steam bath, 47.2 g. (0.4 mole) of ethyl carbonate was added, and the mixture was refluxed for two hours. Then the reaction product was hydrolyzed with ice and acetic acid, treated with an excess of sodium bicarbonate, and extracted with ether. After evaporation of the ether, 33.3 g. (84%) of viscous, oily ester distilling at 121°-123°/0.4-0.5 mm. was obtained. (Reported:[204] 48% yield boiling at 150°-153°/5 mm.)

6-(α-Thienyl)-2-thiouracil

After refluxing a solution of 2.3 g. (0.1 atom) of sodium, 5.3 g. (0.07 mole) of thiourea, and 9.9 g. (0.05 mole) of ethyl β-(2-thienyl)-β-oxopropionate in 50 ml. of absolute ethanol for

---

203. Stadnikoff and Goldfarb, Ber., 61, 2341 (1928).

204. Levine and Hauser, J. Am. Chem. Soc., 66, 1769 (1944).

twenty-four hours, the excess ethanol was removed under reduced pressure from the white precipitate which formed. The residue was dissolved in 50 ml. of water, filtered, and carefully acidified, first with 4.4 ml. of concentrated hydrochloric acid and then with acetic acid in excess, to precipitate the product. After recrystallizing the dry precipitate twice from glacial acetic acid, 3.2 g. (30.5%) of beautiful, tan needles was secured, decomposing at 293°-296°, unchanged by further recrystallization.

Anal. Calcd. for $C_8H_6ON_2S_2$: N, 13.3%.
Found: N, 13.6%.

2-(p-Nitrobenzylmercapto)-4-hydroxy-6-methylpyrimidine

A suspension of the sodium salt of 6-methyl-2-thiouracil was prepared by digesting 7.1 g. (0.05 mole) in a solution of 1.15 g. (0.05 atom) of sodium in 100 ml. of absolute ethanol for two hours. Then 8.58 g. (0.05 mole) of p-nitrobenzyl chloride dissolved in 100 ml. of absolute ethanol was added, and the mixture was refluxed with stirring for six hours. A voluminous precipitate, obtained on cooling, was filtered off and washed with water until all the salt was removed (silver nitrate test). Fine, white powder, 12.3 g. (89%), was obtained melting at 220°-221° unchanged by crystallization.

Another run of the same size using less pure materials gave 6.5 g. (47%) melting at 220°-222° after crystallization from dioxane diluted with n-propanol to incipient crystal

formation.

Anal. Calcd. for $C_{12}H_{11}O_3N_3S$: S, 11.56%.
Found: S, 11.32%.

2-(p-Nitrophenethylmercapto)-4-hydroxy-6-methylpyrimidine

p-Nitrophenethyl bromide was prepared after the method of Sobotka[205] by nitrating phenethyl bromide at -55° (internal temperature) with fuming nitric acid (d. 1.49). The yield of pure product, melting at 66°-67°, from a 0.3 mole run was 18.7 g. (27%). No attempt was made to work up the semi-solid by-product.

A solution of 11.5 g. (0.05 mole) p-nitrophenethyl bromide in 100 ml. of absolute ethanol was stirred at reflux temperature for six hours with a suspension of 0.05 mole of the sodium salt of 6-methyl-2-thiouracil in 100 ml. of absolute ethanol. The heavy, white precipitate formed was filtered off, washed well with water, and crystallized several times from mixtures of n-propanol and dioxane. The yield of the fine, white needles obtained was 9 g. (62%). The crystals soften at 222° and melt at 224°-226° with slow decomposition.

Anal. Calcd. for $C_{13}H_{13}O_3N_3S$: S, 11.00%.
Found: S, 11.08%.

---

205. Sobotka, Ber., 62, 2192 (1929).

Attempted Preparation of 2-(p-Aminobenzylmercapto)-4-hydroxy-6-methylpyrimidine

Ten g. (0.036 mole) of 2-(p-nitrobenzylmercapto)-4-hydroxy-6-methylpyrimidine suspended in 200 ml. of dioxane with 2-3 g. of Raney nickel catalyst was shaken under 4 atm. pressure of hydrogen. The amount of hydrogen required for reduction of the nitro group was absorbed in about five hours. The catalyst was filtered off and the solvent removed under reduced pressure. A hard, red glass softening above 110° was obtained which could not be crystallized. It was ground to a resinous, yellow powder, dried at 110° in vacuo over phosphorus pentoxide, and analyzed.

Anal. Calcd. for $C_{12}H_{12}ON_3S$: S, 12.97%.

Found: S, 10.83%.

Attempted Preparation of 2-(p-Aminophenethylmercapto)-4-hydroxy-6-methylpyrimidine

Seven g. (0.024 mole) of 2-(p-nitrophenethylmercapto)-4-hydroxy-6-methylpyrimidine suspended in 150 ml. of warm dioxane with 2-3 g. of Raney nickel was shaken under 4 atm. of hydrogen. The amount of hydrogen necessary for reduction of the nitro group was taken up, then hydrogenation ceased. The catalyst was filtered from the otherwise clear solution. Then the solvent was distilled in vacuo leaving an orange, vitreous mass, insoluble in ether and ethanol, which could not be crystallized. It melted ca. 55°-70°. It was dried in vacuo

at 110° over phosphorous pentoxide, ground to a resinous powder and analyzed.

Anal. Calcd. for $C_{13}H_{15}ON_3S$: S, 12.27%.
Found: 11.17%.

D. Miscellaneous Compounds

2-n-Butyl-4-methylpyridine

In the course of studying the effect of butyllithium on γ-picoline at various temperatures, 23 g. (0.25 mole) of γ-picoline in 75 ml. of anhydrous ether was added dropwise with stirring to an equivalent amount of 0.94 molar butyllithium in ether, which was maintained at -10° in an ice salt bath. A yellowish precipitate formed. After one and one-half hours of stirring the mixture was carbonated by pouring jet-wise into a slurry of dry ice and ether. After the dry ice had evaporated, the mixture was extracted with 20% sodium hydroxide solution. On acidifying the alkaline extract only a very small amount of red gum was obtained. The alkali-insoluble portion was an oil, which was dried over barium oxide and distilled. About 5 g. of material, obviously the anil addition product of n-butyllithium to γ-picoline, was obtained boiling at 200°-202°/740 mm. A Siwoloboff boiling point determination gave good, reproducible values at 201°-202°.

N_D^{20} 1.4778 Sp. Gv.$_{27}^{27}$ 0.885.

Anal. Calcd. for $C_{10}H_{15}N$: N, 9.39.
Found: N, 9.50.

The picrate was prepared in boiling ethanol, giving bright, yellow crystals melting at 88.5°-90.5° after two crystallizations from ethanol.

Anal. Calcd. for $C_{16}H_{18}O_7N_4$: N, 14.8%.
Found: N, 14.9%.

Treating butyllithium with γ-picoline at -80° followed by carbonation of the reaction mixture resulted in the formation of valeric acid as the only isolable product. Evidently no reaction took place between the first two compounds at that temperature.

2-(α-Thienyl)-6-methoxyquinoline

Thiophene, 30.3 g. (0.36 mole) in 100 ml. of anhydrous ether, was metalated with 0.3 mole of butyllithium in the conventional apparatus under a nitrogen atmosphere. Then 34 g. (0.214 mole) of 6-methoxyquinoline in 60 ml. of ether was added dropwise to the stirred α-thienyllithium at such a rate as to maintain reflux. A greenish-white precipitate formed. After stirring the mixture for one hour, it was hydrolyzed carefully with 200 ml. of water.

The ether phase was separated, mixed with 25 ml. of nitrobenzene to oxidise the dihydroquinoline, and distilled. A fraction (nitrobenzene, aniline, thiophene) was collected at 90°-105°/18 mm. Then 26 g. (a 75% recovery) of 6-methoxy-

quinoline was obtained boiling at 105°-114°/18 mm. (Its identity was checked by preparing its picrate and comparing with the picrate prepared from an authentic sample of 6-methoxyquinoline. Both melted at 217°-218°, with no depression on mixing.) A final fraction of 3.5 g. (6.8%) boiling 200°-210°/18 mm. was collected and crystallized from a benzene and ligroin mixture. Melting point, 137°-138.5°.

Anal. Calcd. for $C_{14}H_{11}ONS$: N, 5.81%.
Found: N, 5.69%.

A picrate of the product was prepared and recrystallized from ethanol. The melting point was 190.5°-192°.

Anal. Calcd. for $C_{20}H_{14}O_8N_4S$: N, 11.9%.
Found: N, 11.75%.

1-(Dimethylaminomethyl)-2-hydroxydibenzofuran

To 9.2 g. (0.05 mole) of pure 2-hydroxydibenzofuran and 11 ml. (0.056 mole) of 23% aqueous dimethylamine solution dissolved in 50 ml. of ethanol, 4.5 ml. (0.06 mole) of formalin was added dropwise with stirring over a one-hour period. Then the mixture was heated to 90° on the water bath for one hour and allowed to cool. Beautiful, white crystals deposited, which were filtered off, washed and dried. The yield was 10.5 g. (87.5%) melting sharply at 114°-115°.

Anal. Calcd. for $C_{15}H_{15}O_2N$: N, 5.81%.
Found: N, 5.70%.

2-(p-Hydroxyphenyl)quininic Acid

N-(p-Hydroxybenzylidene)-p-anisidine was readily prepared by condensing p-hydroxybenzaldehyde and p-anisidine in warm ethanolic solution. Melting point, 214°-215°.

Pyruvic acid, 34.3 g. (0.44 mole), was slowly dropped into a stirred and refluxing mixture of 97 g. (0.427 mole) of the above-mentioned anil in 1200 ml. of ethanol over a one hour period. By the time one-half of the pyruvic acid was added, all the anil had gone into solution. The solution was refluxed four hours more, during which time it was concentrated to 300-400 ml. On cooling, a mass of yellowish-red crystals separated, which were filtered off, washed, and dried. The yield was 29 g. (47.2%) of product decomposing ca. 305°-310°.

Anal. Calcd. for $C_{17}H_{13}O_4N$: N, 4.75%.

Found: N, 4.76%.

IV. DISCUSSION

A. Diphenyl Sulfides and Sulfones

General

The 4-aminophenylsulfonyl group has been found to be one of the most effective groups for conferring antituberculous properties upon a compound (see pp. 19-25). Therefore, it appeared to be of considerable interest to examine a series of substituted aminodiphenyl sulfones and discover the effect of various substituents on their antituberculous activity. To this end a series of both aminodiphenyl sulfides and sulfones and related compounds were synthesized and submitted for testing. It is of interest to note (see below) that in most cases the aminodiphenyl sulfides were more effective than the sulfones.

Method of Testing

The diphenyl sulfides and sulfones prepared in the course of these investigations have been tested or are being tested *in vitro* for tuberculocidal activity by Dr. Guy P. Youmans of the Northwestern University Medical School, Chicago, Illinois. While the *in vitro* activity of a potentially antituberculous drug is of doubtful significance in evaluating its possible activity *in vivo*, nevertheless, some rapid and economical

method for screening large numbers of compounds to select those apparently most likely to be of value must be resorted to.[206] The elaborate and pharmacologically correct testing procedure of Feldman and Hinshaw[207] requires far too much drug, time, and expense to be used in rapid, exploratory investigation of large, new classes of compounds; moreover, the more rapid animal tests being developed are not, as yet, reliable indices of the true in vivo activity of antituberculous drugs.[206]

Tuberculocidal Activity

The currently available results of the tests for tuberculocidal activity of the diphenyl sulfides and sulfones, whose preparation has been described in this dissertation, are tabulated below. Since the virulence of the organisms being used for the tests varies from one series of cultures to another, the numerical value of the activity indices of the compounds being tested will vary also; therefore, these results have arbitrarily been calculated to a common basis. 4,4'-Diaminodiphenyl sulfone, the base drug against which these compounds were compared, has been arbitrarily assigned an activity of 100 for the purposes of this table.

---

206. Burger, J. Chem. Ed., 22, 587 (1945).

207. Feldman and Hinshaw, Am. Rev. Tuberc., 51, 582 (1945).

TABLE II

Diphenyl Sulfides

Name of Compound	Activity
4'-Methyl-2-nitro	<6.25
4-Nitro	<6.25
3'-Methyl-4-nitro	<6.25
4'-Methyl-4-nitro	<6.25
4'-Chloro-4-nitro	400
4'-Isopropyl-4-nitro	1600
3'-Methyl-2,4-dinitro	<50
4'-Chloro-2,4-dinitro	25
2'-Methyl-2-amino	12.5
3'-Methyl-2-amino	25
4-Amino	200
2'-Methyl-4-amino	50
3'-Methyl-4-amino	300
3'-Methyl-4-ureido	100
4'-Chloro-4-amino	<25
3'-Methyl-2,4-diamino	50
4'-Chloro-2,4-diamino	100
4'-Isopropyl-2,4-diamino	50
2'-Methyl-2-(2,5-dimethyl-1-pyrryl)	<6.25

TABLE II (Continued)

Name of Compound	Activity
4'-Methyl-2-(2,5-dimethyl-1-pyrryl)	6.25
4-(2,5-Dimethyl-1-pyrryl)	6.25
3'-Methyl-4-(2,5-dimethyl-1-pyrryl)	6.25

TABLE III

Diphenyl Sulfones

Name of Compound	Activity
4'-Chloro-4-nitro	< 25
4'-Isopropyl-4-nitro	< 25
3'-Methyl-2,4-dinitro	< 12.5
4'-Chloro-2,4-dinitro	50
4'-Isopropyl-2,4-dinitro	50
2'-Methyl-4-amino	25
4'-Methyl-4-amino	< 6.25
4'-Chloro-4-amino	50
4'-Isopropyl-4-amino	50
3'-Methyl-2,4-diamino	100
4'-Chloro-2,4-diamino	50
3'-Methyl-4-(2,5-dimethyl-1-pyrryl)	6.25
4'-Methyl-4-(2,5-dimethyl-1-pyrryl)	6.25

Any attempt to point out correlations between the structures of the various isomeric alkyl, chloro, nitro, and amino substituted diphenyl sulfides and sulfones described in this dissertation, if any correlations do exist, is considerably handicapped by the fact that results of the tuberculocidal tests are available for less than half of the compounds submitted.

In view of the widely held belief that the p-aminophenylsulfonyl group is of outstanding value in conferring valuable antituberculous properties upon a drug, the comparatively high tuberculocidal activity of 4'-isopropyl-4-nitrodiphenyl sulfide (1600) as compared to the corresponding sulfone (<25) and the corresponding amino sulfone (50) is, indeed, surprising. Unfortunately the test on 4'-isopropyl-4-acetylaminodiphenyl sulfide is not available. However, no definite trend is evident indicating that the nitro sulfides are better than the corresponding amino sulfides, for while in one case the former exhibit greater activity than the latter, in two cases the trend is reversed, and in a third they are of equal activity. In the sulfone series, three of the amino derivatives are more active than their nitro precursors, and one has the same activity as its nitro precursor.

In comparing the sulfides with the corresponding sulfones, it is found that in five cases the former are superior, in three cases inferior, and in one case alike. Likewise no

correlation is evident between the 4-nitro and the corresponding 2,4-dinitro derivatives of either series nor between the amines and the corresponding diamines. The 2,5-dimethyl-1-pyrryl derivatives are all less active than their corresponding amino precursors except in one case where little difference exists, and all of them are of low activity. The 4-amino compounds are more active than the 2-amino or 2,4-diamino analogs.

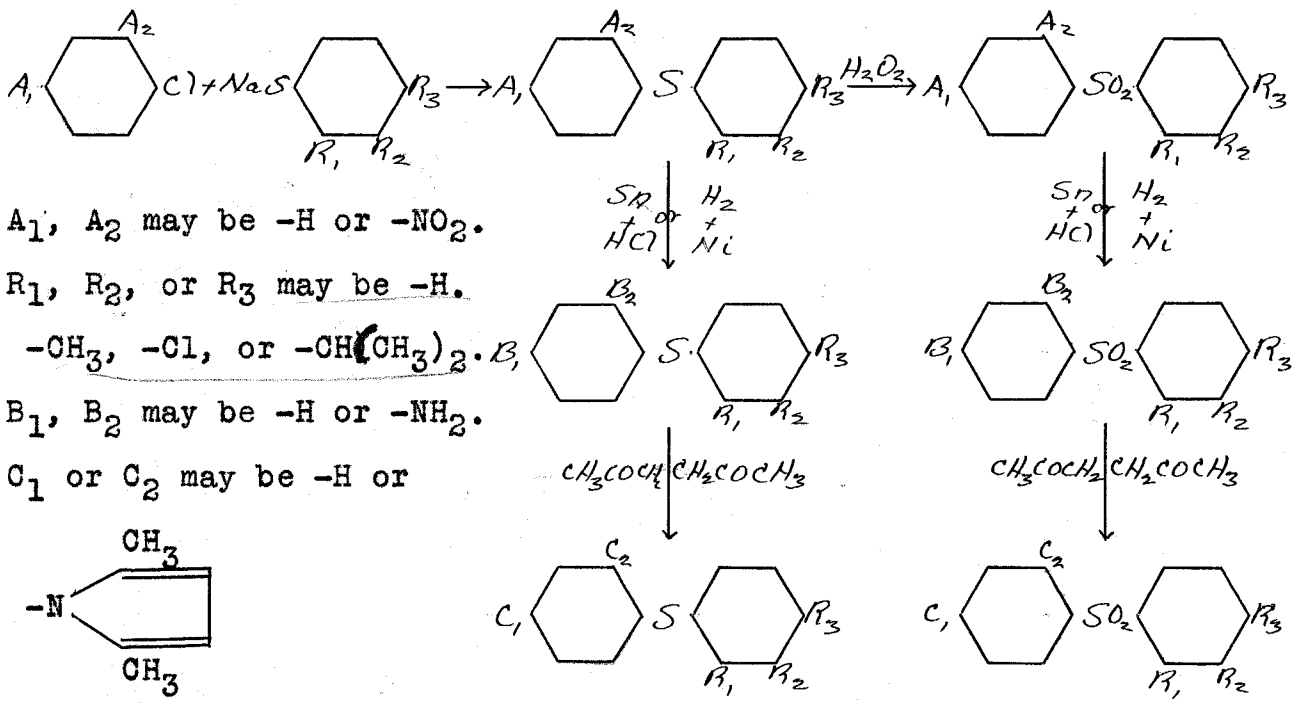
In conclusion, it can be stated that the most definite correlations possible with the meager data available are that an amino group para to the sulfide or sulfone linkage is more effective than one in the ortho position and that conversion of an amino group to a 2,5-dimethyl-1-pyrryl group lessens activity. Other data obtained by the author and others working in these laboratories bear out these conclusions.[208] It scarcely need be emphasized that the data here recorded justify no other generalizations, and that even these two rest on rather insecure foundations insofar as the evidence presented in this dissertation alone is considered. The fact that the majority of the members of this series of compounds have some tuberculocidal activity and that some of them have significantly higher activity than 4,4'-diaminodiphenyl sulfone would seem to justify further investigation in the field of diaryl sulfides and sulfones.

---

208. Unpublished studies.

Methods of Preparation

The general scheme followed in the preparation of the diphenyl sulfides and sulfones described herein is outlined below.



A_1, A_2 may be -H or $-NO_2$.

R_1, R_2, or R_3 may be -H. $-CH_3$, -Cl, or $-CH(CH_3)_2$.

B_1, B_2 may be -H or $-NH_2$.

C_1 or C_2 may be -H or

The preparation of thiophenols from arylamines through the S-aryl ethyl xanthates is a consistently reliable method usually giving yields in the neighborhood of 50-70%. The o-, m-, and p-chlorothiophenols were prepared in yields of 67%, 65%, and 49%, respectively. The preparation of the new thiophenol, p-isopropylthiophenol was quite conveniently accomplished by the chlorosulfonation of cumene followed by reduc-

tion of the sulfonyl chloride by zinc and sulfuric acid in 63.5% overall yield.

Only those aryl halides having a halogen activated by the presence of such groups as the nitro group in their o- and/or p-positions are sufficiently reactive to react with sodium thiophenoxides forming sulfides under ordinary conditions.

Using o-nitrochloro(bromo)benzene, p-nitrochloro(bromo)-benzene, and 2,4-dinitrochlorobenzene, condensed with thiophenol, o-, m-, and p-thiocresols, o-, m-, and p-chlorothiophenols, and p-isopropylthiophenol, a series of new, substituted nitrodiphenyl sulfides have been prepared. 2-Nitrochlorobenzene usually requires from one-half to one hour for complete reaction with the sodium thiophenoxide in boiling ethanol, 4-nitrochlorobenzene requires about three hours, and 2,4-dinitrochlorobenzene requires no more than fifteen minutes. In the last case, more prolonged refluxing often results in the formation of a very much poorer product. For instance, m-thiocresol reacting at reflux temperatures for thirty minutes with 2,4-dinitrochlorobenzene yielded only tar, whereas, when the reactants were just heated to reflux in ethanolic solution and cooled, a 64.5% yield of 3'-methyl-2,4-dinitrochlorobenzene was obtained.

Tarry reduction products of the nitrohalobenzenes caused by the reducing action of the alkaline thiophenol always tend to form; however, the amount is usually small varying somewhat

from one compound to another in a rather unpredictable manner. m-Thiocresol was the most troublesome in this respect and the chlorothiophenols the least so. All of the nitrodiphenyl sulfides are conveniently crystallized from ethanol or methanol.

The diphenyl sulfones were all prepared in very good yields by oxidizing the nitro sulfides with an excess of 30% hydrogen peroxide in glacial acetic acid solution at steam-bath temperatures. Although the primary purpose of these syntheses was to secure aminodiphenyl sulfides and sulfones, the nitro sulfides were oxidised to the sulfones, which were then reduced, rather than by following the alternative route of first reducing the nitro sulfides, acetylating them, oxidising them to the sulfones, and finally deacetylating them to secure the desired product. The latter method involves more steps, the yields are poorer, and the reactions are less clean-cut. Hydrogen peroxide is the reagent of choice for oxidizing sulfides to sulfones. It is more convenient to use, and its action is less drastic and more selective than other commonly used reagents, such as potassium permanganate and chromic acid. Frequently, the nitro sulfones were obtained directly following oxidation in a very pure form scarcely requiring recrystallization at all to bring them to their maximum melting point. The nitro sulfones were readily crystallized from dilute acetic acid, ethanol, or ethanol-benzene mixtures.

The reduction of nitro compounds to amines by means of tin and hydrochloric acid suffers, in general, from the frequent difficulty encountered in liberating the amine from its complex formed with chlorostannous or chlorostannic acid and in separating the amine from the tin-containing residues following the addition of alkali, because of the tendency for colloidal suspensions containing tin compounds to form. This difficulty was encountered in preparing several of the amines described in this thesis.

In the past catalytic reduction of sulfur-containing compounds has been regarded as impracticable because of the poisoning of the catalyst that frequently takes place. Deem and Kaveckis[209] describe the poisoning of Raney nickel during the hydrogenation of various substances in the presence of sulfur compounds of various degrees of oxidation. Mozingo et al.[210] state that Raney nickel is not generally useful for the hydrogenation of sulfur-containing compounds because of the hydrogenolysis to hydrogen sulfide and aryl hydrocarbons that occurs when diaryl sulfides are warmed with rather large amounts of Raney nickel.[211] They did find, however, that supported palladium catalyst was active in hydrogenating

---

209. Deem and Kaveckis, Ind. Eng. Chem., 33, 1373 (1941).

210. Mozingo, Harris, Wolf, Hoffhine, Easton, and Folkers, J. Am. Chem. Soc., 67, 2092 (1945).

211. Mozingo, Wolf, Harris, and Folkers, ibid., 65, 1013 (1943).

sulfur-containing compounds under some conditions, but that the hydrogenolysis of nuclear halogens usually accompanying the use of palladium readily takes place. On the other hand, Morgan and Hamilton[212] report a single instance wherein they reduce p-nitrophenyl β-hydroxyethyl sulfide to the amine in 99% crude yield using Raney nickel catalyst. However, the author's experience has been that nitrodiaryl sulfides and sulfones can be readily reduced to the corresponding amines in excellent yields with small amounts of Raney nickel catalyst at room temperature using hydrogen under one to four atmospheres pressure. In the seventeen cases reported in this thesis, the average yield by catalytic reduction of as little as 0.01 mole to as much as 0.25 mole was 78% after recrystallizing the extremely soluble products to a constant melting point. The crude yields appeared to be well nigh quantitative. In only one case was difficulty encountered in reduction (see pp. 88-89). Even then, other samples of the same compound were reduced with complete success. Since the completion of most of this work, two reports have become available wherein nitrodiaryl sulfones have been reduced to amines using Raney nickel.[37,213]

Some of the nitro compounds were reduced in ethanolic solution with tin and hydrochloric acid; however, as soon as

---

212. Morgan and Hamilton, ibid., 66, 874 (1944).

213. Burton and Hoggarth, J. Chem. Soc., 14 (1945).

the success of the catalytic reduction procedure became apparent, all of them were reduced thereafter in this way. In addition to giving better yields, the process is quicker, more economical, requires less attention, and gives a cleaner, more easily purified product with less side reactions.

In attempting the preparation of two diamino sulfones, 3'-chloro-2,4-diaminodiphenyl sulfone and 4'-isopropyl-2,4-diaminodiphenyl sulfone, and calculated amount of hydrogen for reduction of the nitro groups was smoothly taken up, but the solutions of the amines were so labile in the presence of air that no pure products were isolated. It appears highly probable, however, that by exercising due precautions these compounds could be prepared by catalytic reduction of the nitro compounds.

The aminodiphenyl sulfides and sulfones prepared in the course of these investigations were all very soluble in ethanol and even more soluble in benzene. The most generally suitable solvent for crystallization was found to be ethanol diluted with water. The ratio of the two solvents to one another and to the amount of solute was often a critical factor in effecting crystallization rather than oiling out of the low melting amines, which had a pronounced tendency to oil out of solutions containing too much water.

Three acylated derivatives of 3'-methyl-4-aminodiphenyl sulfide, one of the most promising compounds in this series

in early reports, were prepared to investigate the effects of acylation on the tuberculocidal activity of the amines. They were the formylamino, acetylamino, and ureido derivatives. Heymann and Fieser[102] have prepared a series of symmetrically acylated and alkylated derivatives of 4,4'-diaminodiphenyl sulfone. They found that 4,4'-bis(formylamino)diphenyl sulfone showed promising activity against avian malaria, and that it was less toxic than the parent compound. It was not tested against tuberculosis.

The 2,5-dimethyl-1-pyrryl derivatives were prepared from a number of the aminodiphenyl sulfides and sulfones by condensing them with acetonylacetone.

No correlations are evident between the melting points and the gross molecular structure of the diphenyl sulfides and sulfones prepared, except that in every case the sulfones are higher melting than the corresponding sulfides, as would be expected. One interesting observation was the strikingly high melting point of 4'-isopropyl-4-aminodiphenyl sulfone (154.5°-155.5°) compared with the corresponding sulfide (never isolated as a solid) and nitro sulfone (109°-111°) in contrast to similar relationships among the same derivatives of other alkyl- and chlorodiphenyl sulfides and sulfones.

The preparation of 2,4-dinitrophenyl sulfides and sulfones is a convenient method for derivatizing thiophenols and mercaptans.[82] Those prepared in these investigations further

extend the number of known derivatives available for reference in characterizing thiols by this method.

B. Quinoxalines

General

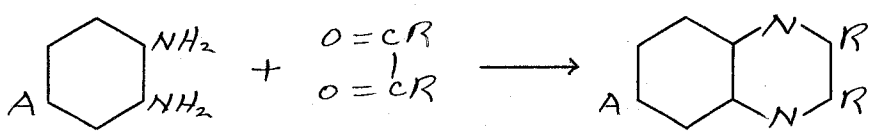
By far the most promising antimalarials discovered in the course of the very extensive researches conducted toward this end in the last thirty years have been basically substituted nitrogen-containing heterocycles. Moreover, the "sulfa" drugs have also shown considerable antimalarial activity. One of the most effective "sulfa" drugs known is sulfaquinoxaline. For these reasons and also because relatively very few basically substituted quinoxalines have been described in the chemical literature and even fewer have been tested for antimalarial activity, a series of substituted aminoquinoxalines and their 2,5-dimethyl-1-pyrryl derivatives have been prepared and subjected to pharmacological testing. In addition, the rather high tuberculocidal activity of some related types of compounds,[214] prompted the synthesis of 2,3-bis(p-aminophenyl) quinoxaline, 2,3-bis(p-hydroxyphenyl)quinoxaline and 2,3-bis-(p-hydroxyphenyl)-6-aminoquinoxaline.

---

214. Unpublished work by J. T. Edwards and R. Clark of these laboratories.

Methods of Synthesis

The quinoxaline nuclei of the quinoxalines synthesized in the course of these investigations were prepared by condensing appropriately substituted α-diketones with substituted o-phenylenediamines according to the following scheme:



A = H, NH_2

R = Alkyl or substituted aryl group

The method of Hinsberg,[187] which was the one first employed in these studies, for preparing 1,2,4-triaminobenzene by reduction of 2,4-dinitroaniline with tin and hydrochloric acid, suffers from all the usual disadvantages of tin and hydrochloric acid reductions. The complex formed between the amine and chlorostannous(ic) acids is often difficult to decompose completely and a tin-containing product is then secured, which is only difficultly purified by recrystallization. In addition, the long and frequent exposure to the air entailed in this process is deleterious to the very easily oxidised polyamine. In order to circumvent these difficulties, the catalytic reduction of 2,4-dinitrobenzene in ethanolic solution over Raney nickel catalyst was developed. The latter method

is much more rapid, convenient, and less expensive than the former, and it yields the product desired in greater yields of at least equal purity. From a series of six catalytic reductions the yields were 81%, 86%, 93%, 86%, 98%, and 85%, respectively. By the other method the yields were 41% and 71.5% on two different runs.

The successful preparation of benzoins in good yields depends on the nature of the substituent groups of the aromatic aldehyde being condensed,[190] on the purity of the reactants, the proportion of water to ethanol in the solvent, and upon avoidance of contact with the air. In particular, acid-free aldehyde and cyanate-free cyanide are essential to success.[188] The yields obtained vary in the vicinity of 40% to 60% in many cases. Often it is difficult to induce crystallization of the benzoins.[215] In these researches crystalline anisoin was secured with some difficulty (96% pure potassium cyanide was the best available) in 40% and 43% yields by one modification of the condensation and in 22% yield by another. From o-chlorobenzaldehyde the condensation with potassium cyanide yielded an oily product which did not readily crystallize.

From the oxidation of anisoin to anisil by means of Fehling's solution, Van Alphen[215] secured only a 44% yield, but he obtained a 61% yield by using alkaline permanganate

---

215. Van Alphen, Rec. trav. chim., 48, 1112 (1929).

oxidation. Boster[216] claims a quantitative yield on oxidizing ansoin to anisil with Fehling's solution. A modification of the method of "Organic Syntheses" for preparing benzil from benzoin using copper sulfate and pyridine as the oxidising agent[217] was developed in the course of these researches and used with complete success. Anisoin was easily and conveniently oxidised to anisil in yields of 96%, 96%, and 100% in three different runs, respectively. The product was obtained in a very pure form without further purification.

The crude product from the preparation of 2,2'-dichlorobenzoin (Hodgson and Rosenberg[190] obtained a 40% yield of crystalline product) was oxidized by the same method to give a 39% overall yield of pure benzil.

The method of Schönberg and Kraemer[193] for preparing 4,4'-dihydroxybenzil by the demethylation of anisil requires the use of hydrobromic acid of 1.78 density, which is not available commercially so far as is known. Neither constant boiling aqueous hydrobromic acid (d. 1.48, 48%) nor 33% hydrogen bromide in acetic acid was found to be efficacious, alone, in the demethylation of anisil; however, the use of equal parts of the two acid solutions was found to smoothly cleave the methoxy groups from anisil resulting in a good yield of pure 4,4'-dihydroxybenzil.

---

216. Boster, Ber., 14, 327 (1881).

217. Clarke and Dreger, Organic Syntheses, Coll. Vol. I, 87 (1941).

The α-diketones were condensed with o-phenylenediamine in glacial acetic acid solution while with 1,2,4-triaminobenzene dihydrochloride, an aqueous solution was employed in the synthesis in which diacetyl was used, and 50-60% ethanol solutions in the syntheses in which the various benzils were used. In all cases the yields were satisfactory, although removal of the resinous by-products in the condensations with 1,2,4-triaminobenzene often entailed two to three crystallizations of the product.

The 2,5-dimethyl-1-pyrryl derivatives of various heterocyclic amines have given evidence of antimalarial activity. For this reason the 6-(2,5-dimethyl-1-pyrryl) derivatives of some of the 6-aminoquinoxalines were prepared by condensing them with acetonylacetone in ethanolic solution with glacial acetic acid as the catalyst.

Both the 6-aminoquinoxalines and the corresponding 2,5-dimethyl-1-pyrryl derivatives were purified by recrystallization from mixtures of benzene and ethanol. An interesting observation on the effect on molecular structure on solubility is afforded by the 2,3-diphenyl-, bis(p-methoxyphenyl)-, and bis(o-chlorophenyl)-6-aminoquinoxalines and their pyrryl derivatives. The amino compounds are very soluble in ethanol and only moderately soluble in benzene whereas the corresponding pyrryl compounds are almost completely insoluble in hot ethanol and exceedingly soluble in hot benzene.

2,3-Bis(p-aminophenylquinoxaline) has been prepared by Kuhn and co-workers[192] by condensing 4,4'-diaminobenzil with o-phenylenediamine; however, the preparation of 4,4'-diaminobenzil involves the rather delicate operation of reducing 4,4'-dinitrobenzil to the aminobenzil without producing unduly large amounts of the corresponding benzoin. In order to circumvent this step, 4,4'-dinitrobenzil was condensed with o-phenylenediamine to form 2,3-bis(p-nitrophenyl)quinoxaline. Mizzoni and Spoerri[147] report getting only resinous products on catalytically reducing 7-methoxy-5-nitroquinoxaline; however, the catalytic reduction of 2,3-bis(p-nitrophenyl)-quinoxaline with Raney nickel catalyst at room temperature under 3 atm. of hydrogen successfully yielded the compound sought, 2,3-bis(p-aminophenyl)quinoxaline.

The 6-aminoquinoxalines are all very strongly fluorescent when dissolved in organic solvents even in extremely dilute solutions, being red by transmitted light and yellowish-green by reflected light.

2,3-Bis(p-hydroxyphenyl)-6-aminoquinoxaline dissolves in acids giving a bright, cherry red solution and in bases giving a brilliant yellow solution. The color change is reversible between a pH of 3.4-3.6, hence it could serve as an acid-base indicator.

Pharmacological Activity

These compounds were tested against avian malaria as a part of the antimalarial program carried out under the direction of the National Defense Research Committee during the war. The methods used have been discussed by Tolman.[218] The results obtained on these tests are still restricted. They are to be published as a monograph by the Government.

A number of the quinoxalines were likewise examined for tuberculocidal activity *in vitro*. The activities of those for which the results are available, calculated to the same basis as those in the preceding section, are as follows:

2,3-dimethyl-6-aminoquinoxaline	200
2,3-bis(*p*-methoxyphenyl)-6-(2,5-dimethyl-1-pyrryl)-quinoxaline	<35
2,3-diphenyl-6-(2,5-dimethyl-1-pyrryl)quinoxaline	25
2,3-bis(*p*-chlorophenyl)-6-(2,5-dimethyl-1-pyrryl)-quinoxaline	50

C. Thiouracils

General

Considerable interest has developed within the last few years in the medical profession in the treatment of hyperthyroid disturbances by chemical means. Among the most effective substances employed have been 2-thiouracil and some of

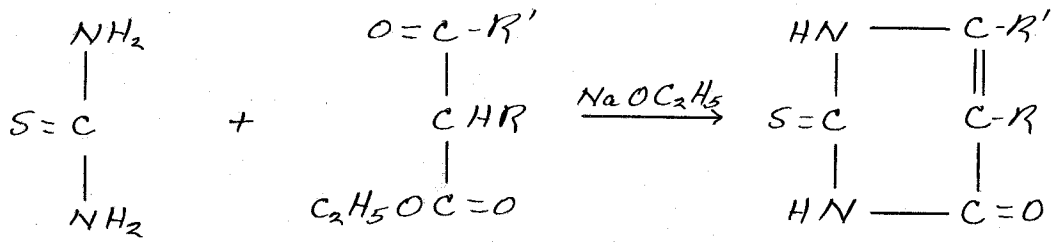
---

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

its derivatives. Since investigations were already underway for the preparation of nitrogen and sulfur containing compounds such as the basically substituted diphenyl sulfides and sulfones, in which the sulfur atom is driectly attached to an aromatic ring, and the quinoxalines, which are nitrogen heterocycles, it seemed desirable from a chemical standpoint to synthesize a series of 2-thiouracils, in which a sulfur atom is directly attached to a nitrogen heterocycle. These compounds would, then, serve as a bridge between the other types and are being tested for antituberculous as well as antithyroid activity.

Methods of Synthesis

The most generally useful method of synthesizing 2-thiouracils is the condensation of thiourea with β-oxo esters in the presence of sodium ethoxide as indicated below:



Three different methods were employed for the preparation of the necessary β-oxo esters. They are the alkylation of ethyl acetoacetate with alkyl halides in the presence of sodium ethoxide, the Claisen condensation of esters with sodium ethoxide, and the carbethoxylation with ethyl carbonate of

sodio ketones, which had been made by the action of sodamide. The reactions are as follows:

(A) $[\bar{C}H_3COC\bar{H}COOC_2H_5]Na^+ + R'X \longrightarrow CH_3COCHCOOC_2H_5 + NaX$
$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad R'$

(B) $RCOOC_2H_5 + R'CH_2COOC_2H_5 \xrightarrow{NaOC_2H_5} RCOCHCOOC_2H_5 + C_2H_5OH$
$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad R'$

(C) $RCOCH_3 + NaNH_2 \rightarrow [\bar{R}CO\bar{C}H_2]Na^+ + NH_3$

$[\bar{R}CO\bar{C}H_2]Na^+ + (C_2H_5)_2CO_3 \longrightarrow RCOCH_2COOC_2H_5 + NaOC_2H_5$

By the alkylation of sodio acetoacetic ester with γ-diethylaminopropyl chloride, 1-diethylamino-4-carbethoxyhexanone-5 was prepared. This β-oxo ester has been prepared before, but it has been hydrolyzed <u>in situ</u> to the corresponding ketone without isolation. This thesis reports the first isolation, so far as is known, of the pure β-oxo ester and the determination of some of its constants. 1-(γ-Diethylaminopropylmercapto)-3-carbethoxypentanone-4 was prepared by alkylating sodio acetoacetic ester with γ-diethylaminopropyl β-chloroethyl sulfide. Although the latter and its precursor alcohol, γ-diethylaminopropyl β-hydroxyethyl sulfide, have been previously prepared,[194] their refractive indices, densities, and molecular refractions have been determined and reported for the first time.

It was not possible in the course of these researches to successfully condense these two complex β-oxo esters with thiourea to form the 2-thiouracils. Only a polymeric, gummy

residue, quite unlike the probable properties of the expected thiouracils, was obtained. Anderson *et al.*[64] report the formation of unidentified by-products in considerable amount in preparing some of the longer chain (butyl, *n*-amyl, *n*-hexyl) 6-substituted thiouracils. Moreover, in many cases the yields are not high in condensing β-oxo esters with thiourea to form thiouracils.

The α-, β-, and γ-pyridoylacetates were prepared by the Claisen condensation of the pyridinecarboxylic acid esters and ethyl acetate. Although these β-oxo esters have been reported heretofore,[197,199,200] it was found possible to prepare the first two of them in greatly improved yields by a suitable modification of the Claisen condensation procedure involving the use of benzene as a diluent. The preparation of the necessary sodium ethoxide *in situ* in benzene suspension also obviates the necessity of preparing fresh, anhydrous, solid sodium ethoxide for the condensation as is usually done. The isolation of pure liquid ethyl picolinoylacetate does not appear to have been done. Pinner[197] reports that it cannot be accomplished; Burrus and Powell[199] isolated it as its hydrochloride; however, it was found possible to distill the free base (with little decomposition) and isolate the slightly impure liquid, which can be kept for a considerable time with only minor decomposition.

The method of Camps[198] has usually been used in esterifying the pyridinecarboxylic acids. Camps reports yields of 90%, 90%, and 91%, respectively, for the α-, β-, and γ- isomers; however, later workers have never been able to duplicate his yields. Burrus and Powell[199] obtained yields of 61% of ethyl nicotinate and 30% of ethyl isonicotinate by the method of Camps. In the researches herein reported, ethyl nicotinate was obtained in 72% yield by the method of Camps. By employing esterification with anhydrous hydrogen chloride passed into absolute ethanol, ethyl isonicotinate was conveniently secured in 61.4% yield.

The preparation of isonicotinic acid by oxidising γ-picoline with potassium permanganate was conveniently modified by employing more concentrated solutions than are usually used. The rate of heating the reaction must be carefully watched to moderate the vigor of the reaction.

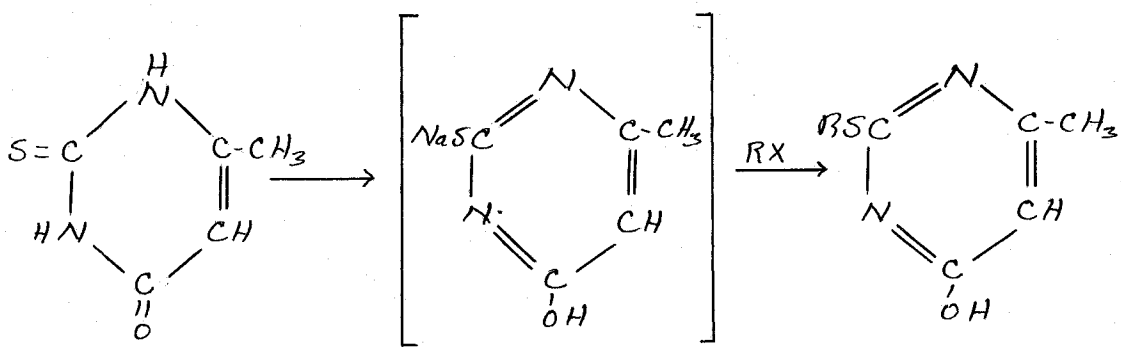
The 6-(α-, β-, and γ-pyridyl)-2-thiouracils were prepared by condensing the appropriate β-oxo esters with thiourea in 29%, 38%, and 50% yields, respectively. They are very high melting solids. They are quite insoluble in organic solvents, but they are readily soluble in strong acids and bases.

Both ethyl p-anisoylacetate and ethyl β-(2-thienyl)-β-oxopropionate were prepared by carbethoxylation of the corresponding ketones with ethyl carbonate by the use of sodamide. This is a convenient method for preparing small amounts of

β-oxo esters where the ketones are available. Ethyl p-anisoylacetate was prepared for the first time by this method. It tends to decompose on distilling evan at low pressures.

6-(p-Methoxyphenyl)-2-thiouracil and 6(α-thienyl)-2-thiouracil were prepared in yields of 31%, and 30.5% respectively. Both are high melting solids, difficultly soluble in organic solvents, but easily soluble in bases.

Mercapto derivatives of 6-methyl-2-thiouracil were prepared as follows:



Neither o-nitrobromobenzene nor p-nitrobromobenzene were found to be sufficiently active to undergo methathesis with a suspension of the sodium salt of the uracil in absolute ethanol, although they will readily condense with ordinary sodium mercaptides under such conditions. The fact that the sodium salt of 6-methyl-2-thiouracil must form from its enolic form, wherein the sulfhydryl group is in competition with the hydroxy group for the sodium, is undoubtedly a contributing factor. All the possibilities for effecting a condensation

were not explored. With 2,4-dinitrochlorobenzene, having an even more active halogen, a product was secured; however, its isolation in a form pure enough to give a correct elementary analysis was not accomplished.

γ-Diethylaminopropyl chloride, p-nitrobenzyl chloride, and p-nitrophenethyl bromide, all of which are substituted alkyl halides in contrast to the aryl halides considered above, condensed easily with the sodium salt to 6-methyl-2-thiouracil forming the corresponding mercapto derivatives.

The attempted preparation of 2-(p-aminobenzylmercapto)-4-hydroxy-6-methylpyrimidine and 2-(p-aminophenethylmercapto)-4-hydroxy-6-methylpyrimidine by the catalytic reduction of their corresponding nitro compounds over Raney nickel catalyst resulted in the formation of resinous polymers containing less than the required amount of sulfur in both cases. The correct amount of hydrogen was absorbed for complete reduction of the nitro groups and then hydrogenation ceased. Johnson and Bailey[157a] report that 2-ethylmercapto-4-hydroxy-5-ethyl-6-methylpyrimidine slowly reacts with aniline in ethanolic solution forming 2-anilino-4-hydroxy-5-ethyl-6-methylpyrimidine. It appears probable, therefore, that the desired aminoaralkyl-mercapto uracils were first formed on reduction, but later polymerized forming the anilino linkage with adjacent molecules to some extent.

Arrangements have been made to have the 2-thiouracil derivatives prepared during these investigations tested for antithyroid activity at the National Institute of Health, Washington, D. C. The results are not yet available. They are also being tested for tuberculocidal activity as described in a preceding section.

D. Miscellaneous Compounds

In the course of studying the effect of butyllithium on γ-picoline at various temperatures, it was observed that no reaction took place at -80°. On carbonation of the reaction mixture a nearly quantitative yield of valeric acid was obtained. At -10°, the n-butylanil addition product formed, which on hydrolysis and mild oxidation of the intermediate dihydro compound yielded the new 2-n-butyl-4-methylpyridine, which was characterized by forming its picrate.

Thiophene was metalated by the action of butyllithium, then the α-thienyllithium formed was used in treating 6-methoxyquinoline in ether at room temperatures. Most of the 6-methoxyquinoline was recovered unchanged, but a small yield of the new 2-(α-thienyl)-6-methoxyquinoline was obtained. Its picrate was prepared as a derivative.

So far as is known, the first successful application of the Mannich reaction to a hydroxydibenzofuran was made in condensing 2-hydroxydibenzofuran, formaldehyde, and dimethylamine together to form what in all probability is the 1-(dimethyl-

aminomethyl)-3-hydroxydibenzofuran.

In the process of investigating cinchophen derivatives as antimalarials, a new derivative 2-(p-hydroxyphenyl)quininic acid was synthesized by the Döbner cinchoninic acid synthesis.

Inasmuch as these compounds are all related to active antimalarial or antituberculous types, their pharmacological activity has been examined. The tuberculocidal activity of 2-(p-hydroxyphenyl)quininic acid is one-fourth that of 4,4'-diaminodiphenyl sulfone whereas 2-(α-thienyl)-6-methoxyquinoline is less than one-fourth as active. 1-(Dimethylaminomethyl)-2-hydroxydibenzofuran is inactive against avian malaria at a quinine equivalent of 0.06. No report is available on 2-n-butyl-4-methylpyridine.

V. SUMMARY

1. General reviews have been made on the chemotherapy of malaria, tuberculosis (from the standpoint of metabolite antagonists), and hyperthyroidism.

2. Surveys have been made of the general methods of preparation of diaryl sulfides and sulfones, quinoxalines, and 2-thiouracils.

3. A series of nitro-, amino-, and 2,5-dimethyl-1-pyrryldiphenyl sulfides and sulfones have been synthesized and submitted for testing for tuberculocidal activity. A new thiophenol, p-isopropylthiophenol was prepared.

4. An improved and generally applicable method of reducing nitrodiphenyl sulfides and sulfones has been developed and extensively tested.

5. Several substituted 6-amino, 6-(2,5-dimethyl-1-pyrryl), and related quinoxalines have been synthesized and submitted for examination as antimalarial and antituberculous agents. One of them, 2,3-bis(p-hydroxyphenyl)-6-aminoquinoxaline acts as an acid-base indicator. Improved methods were worked out for preparing several of the intermediates.

6. Some 2-thiouracil derivatives have been synthesized which are being examined for antithyroid and tuberculocidal activity. During the course of this work two new β-oxo esters

were prepared, and improved methods or techniques for preparing others have been employed.

7. A few miscellaneous heterocyclic derivatives have been synthesized and tested pharmacologically.

8. Complete pharmacological results are not yet available. While many of the compounds for which reports have been received have shown varying activities from slight to quite appreciable, none of them have shown outstanding therapeutic activity.

VI. APPENDIX

The following letter from Dr. E. J. Crane was received in reply to an inquiry regarding the proper method of naming the pyrryl derivatives of the aminodiphenyl sulfides and sulfones, in particular the one mentioned.

COPY

November 10, 1945

Mr. H. Smith Broadbent
Iowa State College
Ames, Iowa

Dear Mr. Broadbent:

I am writing in answer to your letter of November 6. Before doing so I have consulted with Dr. Leonard T. Capell, who specializes in the organic side of our work here.

We would prefer to name this compound as a derivative of pyrrole, which is a nitrogen containing heterocycle. The name would be 2,5-dimethyl-1-[p-(m-tolylmercapto)phenyl]-pyrrole. By using parentheses and brackets one does away with the necessity of using primed numbers. If it is preferred to name the compound as a sulfide, then the name p-(2,5-dimethyl-1-pyrryl)phenyl m-tolyl sulfide is preferred over a name based on diphenyl sulfide as a parent compound.

Sincerely yours,

(Signed) E. J. Crane

EJC:MW