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# Some derivatives of dibenzofuran and dibenzothiophene

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# SOME DERIVATIVES OF DIBENZOFURAN AND DIBENZOTHIOPHENE

by

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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
1952

## ACKNOWLEDGMENT

The author wishes to express his sincere appreciation to Dr. Henry Gilman for helpful advice, criticism and encouragement given throughout the course of this investigation.

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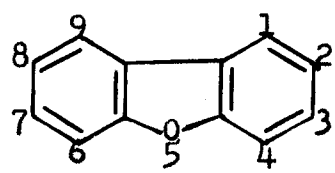
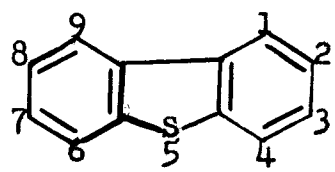
# INTRODUCTION

The literature of dibenzofuran (I) and dibenzothiophene (Ia) is somewhat confusing because of the different systems of numbering employed. The system used in this work and in all recent publications in this country is that adopted in 1937 by Chemical Abstracts.

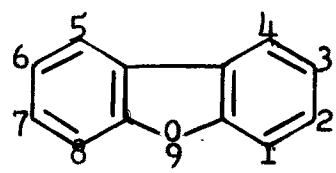



I

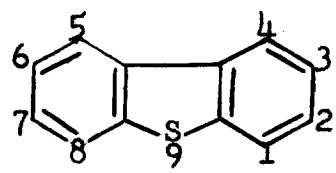



Ia

The numbering system employed by Chemical Abstracts prior to 1937 and that still employed in most countries other than the United States is




II

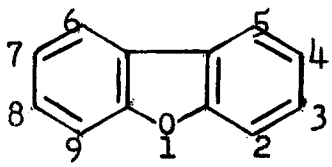



IIa

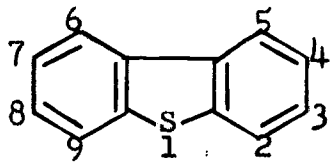
Usually, when the former system (I,Ia) is involved the compound is listed as a derivative of dibenzofuran or dibenzothiophene, while with the latter system (II,IIa) it is described as a derivative of diphenylene oxide or diphenylene

sulfide; this generalization is not infallible, however, especially with the older literature.

A third system of numbering recommended by Professor A. M. Patterson in this country and by Professor M. Richter abroad[1] was prevalent in the literature of the early 1930's (III,IIIa). This system was discarded before it had become common.




III




IIIa

Due to these divergent systems considerable care must be taken when consulting the literature to ascertain the method of numbering.

A brief review of the chemistry of dibenzofuran may be found among Elderfield's heterocyclic volumes.[2] Perhaps for a more complete account of the chemistry of dibenzofuran, and especially for accounts of the problems of orientation and structure proof of derivatives of dibenzofuran and the solutions to these problems one should consult, preferably

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[1] H. Oatfield, Unpublished Master's Thesis, Iowa State College, 1933.

[2] R. C. Elderfield, "Heterocyclic Compounds", John Wiley and Sons, Inc., New York, N. Y., 1951, Vol. 2.

consecutively, dissertations from this laboratory concerning this topic.[1,3,4,5,6,7,8,9,10]

A brief review of the chemistry of dibenzothiophene likewise may be found in Elderfield's Volume II.[2] An additional review can be obtained by consulting works of Jacoby,[11] Avakian,[12] Nobis,[13] and Esmay.[14] A bibliography

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[3] D. M. Hayes, Unpublished Master's Thesis, Iowa State College, 1934.

[4] M. W. Van Ess, Doctoral Dissertation, Iowa State College, 1936.

[5] P. R. Van Ess, Doctoral Dissertation, Iowa State College, 1936.

[6] L. C. Cheney, Doctoral Dissertation, Iowa State College, 1938.

[7] J. Swislowsky, Doctoral Dissertation, Iowa State College, 1939.

[8] H. B. Willis, Doctoral Dissertation, Iowa State College, 1943.

[9] J. R. Thirtle, Doctoral Dissertation, Iowa State College, 1943.

[10] J. A. Hogg, Doctoral Dissertation, Iowa State College, 1944.

[11] A. L. Jacoby, Doctoral Dissertation, Iowa State College, 1938.

[12] S. Avakian, Doctoral Dissertation, Iowa State College, 1944.

[13] J. F. Nobis, Doctoral Dissertation, Iowa State College, 1948.

[14] D. L. Esmay, Doctoral Dissertation, Iowa State College, 1951.

of dibenzothiophene and its derivatives through 1950 may be found in the dissertation of Esmay.[14]

The increased interest in dibenzofuran and dibenzothiophene is evidenced by the increased volume of literature concerning these compounds and their derivatives. It is also noteworthy that a considerable number of patents concerning derivatives of dibenzofuran and dibenzothiophene have been granted in recent years, the chief interests being toward possible pharmaceuticals or dyes.

# HISTORICAL

The purpose of the literature survey to be discussed in the following pages is to furnish a general background of information pertinent to the experimental work carried out during the course of this study. The topics to be discussed are quite broad; thus the following discussion represents an attempt to summarize and correlate the more important information.

The final portion of the literature survey consists of three tables. The first two tables represent a compilation of known dibenzofuran derivatives other than those recorded previously by Swislowsky,[7] Cheney,[6] Willis,[8] and Hogg.[10] The third is an extension of the compilation of known derivatives of dibenzothiophene made earlier by Nobis[13] and Esmay.[14] The literature has been covered through 1951.

## Chemotherapy of Tuberculosis

The chemotherapy of tuberculosis is an interesting topic to follow from its origin to the present. Tuberculosis, despite its complexities, was one of the first diseases to which chemotherapeutic methods were applied. The search for antituberculous agents which followed may be

traced through periods of considerable optimism and through discouraging times requiring much determination in view of the seemingly insurmountable difficulties. This determination is now beginning to pay dividends with the recent significant advances in the treatment of tuberculous patients. With the large background of information now available and the present extensive research, there is little doubt that remarkable achievements will be forthcoming in the next few years.

Tuberculosis, the "white plague" of medieval days, has afflicted mankind since antiquity and has been one of the most fatal of human diseases. In spite of a decline in the incidence and severity of the disease, even today tuberculosis ranks seventh among the causes of death.

The chemotherapy of tuberculosis is a fundamentally different problem from that of the other common diseases. The causative organism, first isolated by Koch in 1882, is Mycobacterium tuberculosis, an acid-fast organism capable of infecting almost any tissue of the body. Unlike causative organisms of almost all other bacterial diseases, the tubercle bacilli rarely appear unprotected in the blood stream. The bacilli are surrounded by three difficultly permeable layers. First, there is the avascular bundle of epithelial cells forming the outer casement of the tubercle. Then, the phagocytic cell, the result of the body's defense

mechanism, which may surround the organism but fail to destroy it. Last, the bacillus itself is surrounded by a waxy coating. It was for a time advocated that any drug in order to be effective must be lipid soluble; however, recent successes have cast some doubt upon this theory. Another complicating factor with tuberculosis is the slow action of the body's defense mechanisms. Though the growth and spreading of the bacteria may be halted by some chemotherapeutic agent, the host is incapable of a rapid destruction of the infectious organism.

Reviews of the chemotherapy of tuberculosis previous to 1946 may be found in the dissertations of Fullhart,[15] Broadbent,[16] and especially Massie.[17,18] In view of these available discussions, this survey will dwell but briefly on the earlier drugs, emphasizing primarily work that has been reported since 1946.

A survey of antituberculous agents should rightfully be

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[15] L. Fullhart, Doctoral Dissertation, Iowa State College, 1946.

[16] H. S. Broadbent, Doctoral Dissertation, Iowa State College, 1946.

[17] S. P. Massie, Doctoral Dissertation, Iowa State College, 1946.

[18] For a complete treatment of all aspects of the chemistry of tuberculosis prior to 1932 see H. G. Wells, L. M. Dewitt and E. R. Long, "The Chemistry of Tuberculosis", 2nd ed., The Williams and Wilkins Co., Baltimore, Maryland, 1932.

divided into two principle categories: antibiotic substances and synthetic agents.

At the present time the greatest success in the treatment of tuberculosis on a large scale can be attributed to antibiotics rather than to synthetic drugs; the reverse was true a few years previous and current promising results indicate an increasing importance of synthetic drugs in the future. For the purpose of clarity it should be mentioned that at the present time the most beneficial treatment involves the combined use of an antibiotic (Streptomycin) and various synthetic antituberculous agents.

Of the hundreds of antibiotics which have been isolated and tested in recent years all but a few have been impractical for tuberculous treatment either due to lack of activity or because of high toxicity. The most important single substance for the treatment of tuberculosis to date is streptomycin[19] or its reduction product, dihydrostreptomycin. The structure of streptomycin has been determined[20,21] as:

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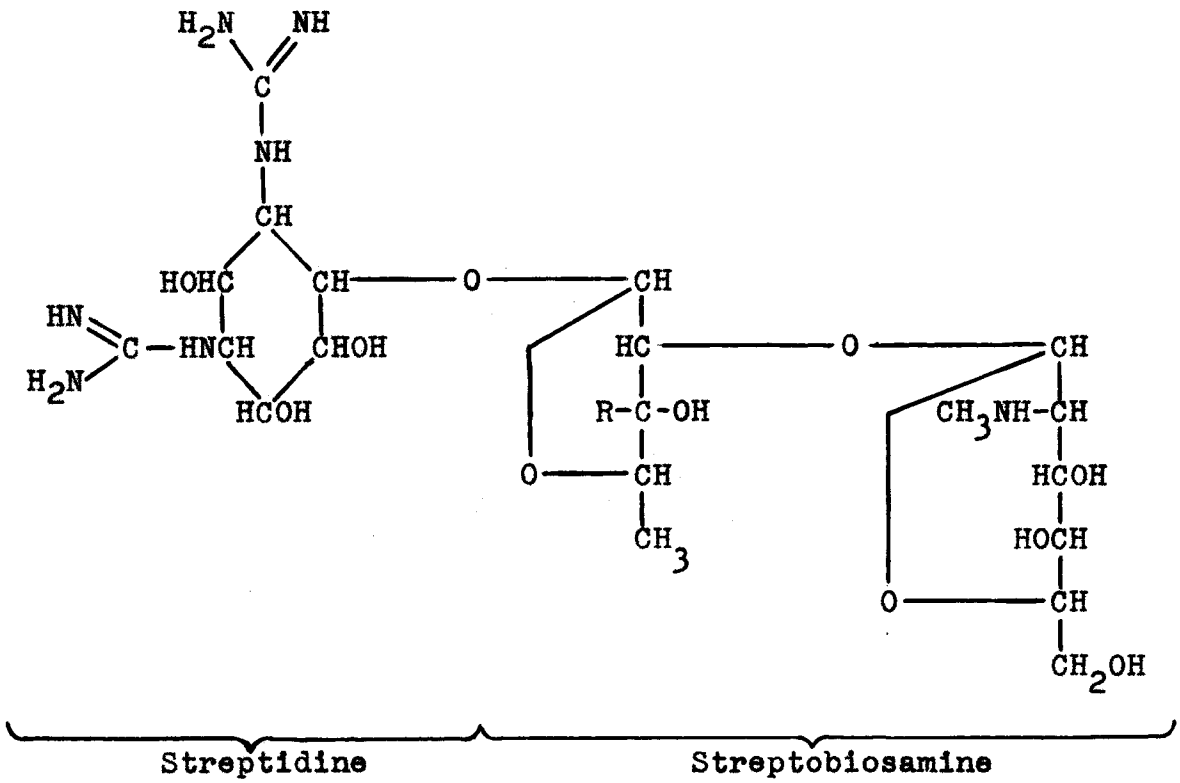
[19] A. Schatz, E. Bugie and S. A. Waksman, Proc. Soc. Exptl. Biol. Med., 55, 66 (1944).

[20] R. L. Peck, R. Graber, A. Walti, E. W. Peel, C. E. Hoffhine, Jr. and K. Folkers, J. Am. Chem. Soc., 68, 1390 (1946).

[21] N. G. Brink, F. A. Kuehl, Jr. and K. Folkers, Science, 102, 506 (1945).




Streptomycin: R = $-\overset{H}{\underset{|}{C}}=O$
Dihydrostreptomycin: R = $-CH_2OH$

Dihydrostreptomycin seems slightly less toxic than the parent aldehyde, possesses the same activity and results in similar side reactions. Also, organisms which are resistant to one are resistant to the other. There is some doubt that the advantage of slightly reduced toxicity justifies the expense incurred in the preparation of the dihydro compound from streptomycin.

Streptomycin, though the best single drug, is not the "cure all" treatment for tuberculosis. Its effectiveness

varies depending upon the type of tuberculosis and the stage at which treatment is begun. The great disadvantages of streptomycin are the injurious side reactions which may accompany its use and especially the rapidity with which resistant strains develop; the latter effect has been partially overcome by the concomitant administration of p-aminosalicylic acid. It is unlikely that the mechanism of action for streptomycin is the same as that for Promine and p-aminosalicylic acid (see later part of this discussion) since these drugs often increase the effectiveness of streptomycin treatment.

Neomycin,[22] a comparatively new antibiotic, shows high antituberculous activity though it seems to possess rather high toxicity. The chemical structure of this substance has not been established; one entity, Neomycin A, has been obtained in pure form.[23] Neomycin A is active against streptomycin-resistant strains of bacteria and it does not seem to give any appreciable rise to the development of resistant organisms. This drug has been effective in extra-pulmonary tuberculosis but has not been very beneficial with pulmonary tuberculosis or tuberculosis meningitis.

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[22] S. A. Waksman and H. A. Lechevalier, ibid., 109, 305 (1949).

[23] R. L. Peck, C. E. Hoffhine, Jr., P. Gale and K. Folkers, J. Am. Chem. Soc., 71, 2590 (1949).

Viomycin[24] whose activity was reported only recently has not yet received sufficient study for a critical evaluation. The properties of this antibiotic are similar to those of Neomycin.

Other antibiotics which possess some tuberculostatic activity, but which have not proved practical either due to low activity or high toxicity are: Lactaroviolin,[25] sodium azulylacrylate,[25] Pyolipic Acid,[26] Fumigatin,[27] Clitocybin,[28] Enniatin,[29] Javanicin,[30] Oxyjavanicin,[30] usnic acid,[31]

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[24] Q. R. Bartz, J. Ehrlich, J. D. Mold, M. A. Penner and R. M. Smith, Am. Rev. Tuberc., 63, 4 (1951).

[25] H. Willstaedt and B. Zetterberg, Svensk. Kem. Tidskr., 58, 306 (1946) [C. A., 41, 2461 (1947)].

[26] A. Stoll, A. Brack and J. Renz, Experientia, 3, 115 (1945).

[27] M. C. McCowen, M. E. Callender and J. E. Lawlis, Jr., Science, 113, 202 (1951).

[28] G. Hollande, Compt. rend., 221, 361 (1945).

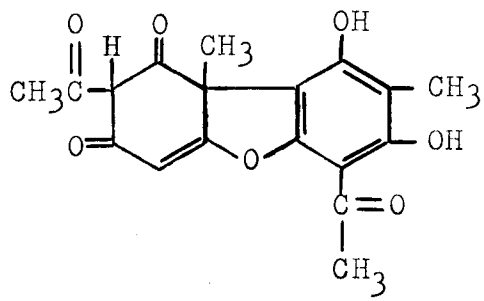
[29] E. Gäumann, S. Roth, L. Ettlinger, P. A. Plattner and U. Nager, Experientia, 3, 202 (1947).

[30] H. R. V. Arnstein and A. H. Cook, J. Chem. Soc., 1021 (1947).

[31] A. Marshak and M. Kuschner, U. S. Pub. Health Repts., 65, 131 (1950).

Diploicin,[32] Streptothricin,[33] Terramycin,[34] Humulone,[35] Lupulone,[35] and Chloromycetin.[36]

In view of this study, the activity of usnic acid[37] is of particular interest. From the structure shown,



Usnic Acid

it will be seen that usnic acid has the skeleton structure of a dibenzofuran derivative. The tuberculostatic activity of usnic acid alone is not great enough to be an effective

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[32] V. C. Barry, Nature, 158, 131 (1946).

[33] E. W. Emmart, ibid., 60, 1415 (1945).

[34] G. L. Hobby, T. F. Lenert, M. Donikian and D. Pikula, Am. Rev. Tuberc., 63, 434 (1951).

[35] Y. C. Chin, H. H. Anderson, A. Alderton and J. C. Lewis, Proc. Soc. Exptl. Biol. Med., 70, 158 (1949).

[36] G. P. Youmans, A. S. Youmans and R. R. Osborne, ibid., 67, 426 (1948).

[37] V. C. Barry, L. O'Rourke and D. Twomey, Nature, 160, 800 (1947).

clinical drug; however, it has been shown to potentiate the effect of streptomycin.[31]

The synthetic antituberculous agents may be divided into eight principal categories: early drugs, benzothiazole derivatives, phenols and aromatic ethers and sulfides, diarylamines, sulfones and sulfonamides, aliphatic acids, thiosemicarbazones, and aromatic and heterocyclic acids and their derivatives.

The early search for effective drugs for tuberculosis was almost entirely empirical. The reviews listed at the beginning of this discussion have considered these early searches for effective compounds; therefore, a detailed account will not be here included.

Table I includes a list of some of the compounds which attracted interest in earlier research upon the chemotherapy of tuberculosis and will give the reader some idea of the diverse compounds which have been employed as antituberculous agents. This Table is taken from two reports by Burger[38,39]; the activity indications are rather arbitrary, a plus sign indicating slight activity, a double plus sign indicating moderate activity, etc.

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[38] A. Burger, First National Medicinal Chemistry Symposium of the American Chemical Society, Ann Arbor, Michigan, June, 1948.

[39] A. Burger, "Medicinal Chemistry", Interscience Publishers, Inc., New York, N. Y., 1951, Vol. 2.

Table I

Some Antituberculous Compounds

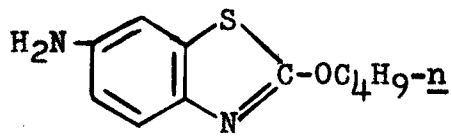
| Compound | Activity |
|---|---|
| **Vitamins and Hormones** | |
| Irradiated Ergosterol | + |
| p-Aminobenzoic acid | ± |
| Ethyl p-aminobenzoate | + |
| Diethylstilbestrol | ± |
| 4,4'-Bis-diethylaminoethoxy-α,α'-diethylstilbene | + |
| **Alkaloids** | |
| Quinine | ± |
| Ethylapoquinicine | + |
| Isoamylapoquinicine | + |
| Isoamylapoquinine | + |
| Aminohydroquinine | ± |
| Ethylapoquinine | ± |
| α-Isoquinine | ± |
| Cepharanthine | +++ |

(Continued on next page)

Table I (Continued)

| Compound | Activity |
|---|---|
| Inorganic and Metalorganic Drugs | |
| $Na_5Au(SP_3)_4$ | + |
| $Na_3AuS_2P_3$ | ++ |
| p-$AuOC_6H_4COONa$ | + |
| Ag-Acriflavin, Ag-Proflavine | ± |
| Ag-Trypan blue | ± |
| $FeCl_3$ | ± |
| Ca-Gluconate | + |
| Calcium phosphate | + |
| Cu-Salicylate | + |
| Au-3,5-Diiodosalicylaldehyde | + |
| Cu-Mercaptobenzimidazoles, -benzoxazoles, etc. | + |
| Cu-Thiourea with Na benzoate | + |
| Cadmium sulfide | + |
| Silica | ± |
| Germanium dioxide | ± |

Several rather simple benzothiazole derivatives have been shown to possess tuberculostatic activity, especially some amino derivatives. 2-n-Butoxy-6-aminobenzothiazole has been shown to be twice as active *in vivo* as 4,4'-diaminodiphenyl sulfone and about three-fourths as effective as streptomycin.[40]




2-n-Butoxy-6-aminobenzothiazole

Other significantly active benzothiazoles include the 2,6-diamino-, the 2-isopropoxy-6-amino-, the 2-ethoxy-6-amino-, the 2-chloro-6-amino-, the 2-methyl-6-amino-, and the 2-mercapto-6-amino- derivatives.[40]

Considerable research has been reported concerning aromatic ethers and sulfides; this material is of particular interest in connection with this study in view of the close structural relationship between the aromatic ethers (or sulfides) and dibenzofuran (or dibenzothiophene).


X = O or S

A very interesting report concerning aminohalodiphenyl ethers is that of Barry, et al.,[37] which is summarized in Table II.

From Table II, the activity of compounds 5 and 6 indicates that the introduction of polar groups such as the amino or carboxyl groups in the para position decreases the effectiveness; however, a halogen atom in either the ortho or para position (compounds 7 and 8) greatly enhances the activity. An amino substituent in the ortho rather than the para position (compounds 4 and 9) or two amino groups result in a considerable loss of activity. Additional halogen substitution (compounds 12, 13 and 14) results in a very marked increased activity, 4-amino-2,2',4',5'-tetrachlorodiphenyl ether being very active. Replacement of the amino group by a carboxyl group (compound 15) results in a slight loss of activity while a similar replacement by an hydroxyl group (compounds 16 and 17) gives increased effectiveness.

Barry also reported 2-chloro (or bromo)-7-aminodibenzofuran to completely inhibit M. tuberculosis at a dilution of 1/400,000.

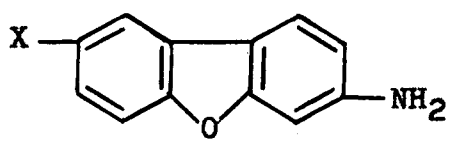
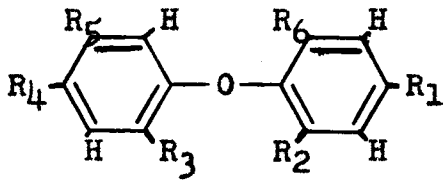



Table III gives the results of the testing of some dibenzofuran and dibenzothiophene derivatives as well as some

Table II

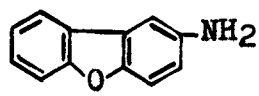
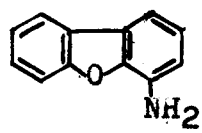
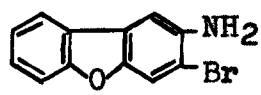
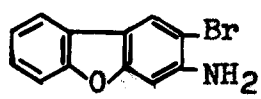
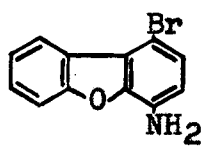
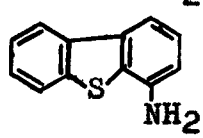
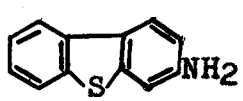
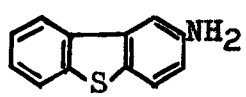
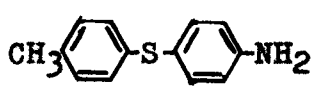
*In vitro* Tuberculostatic Activity of Some Diphenyl Ethers[37]




| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | Complete inhibition of *M. tuberculosis* |
|---|---|---|---|---|---|---|---|
| 1 | $NH_2$ | H | H | H | H | H | 1/35,000 |
| 2 | $SO_3H$ | H | H | H | H | H | 1/5,000 |
| 3 | COOH | H | H | H | H | H | 1/1,000 |
| 4 | H | $NH_2$ | H | H | H | H | 1/10,000 |
| 5 | $NH_2$ | H | H | $NH_2$ | H | H | 1/4,000 |
| 6 | $NH_2$ | H | H | COOH | H | H | 1/6,000 |
| 7 | $NH_2$ | H | H | Cl | H | H | 1/110,000 |
| 8 | $NH_2$ | H | Cl | H | H | H | 1/150,000 |
| 9 | H | $NH_2$ | H | Cl | H | H | 1/15,000 |
| 10 | $NH_2$ | $NH_2$ | H | Cl | H | H | 1/20,000 |
| 11 | $NH_2$ | $NH_2$ | Cl | Cl | Cl | H | 1/25,000 |
| 12 | $NH_2$ | H | Cl | Cl | H | H | 1/600,000 |
| 13 | $NH_2$ | H | Cl | Cl | Cl | H | 1/1,000,000 |
| 14 | $NH_2$ | I | H | Cl | H | I | 1/225,000 |
| 15 | COOH | H | H | Cl | H | H | 1/25,000 |
| 16 | OH | H | H | H | H | H | 1/100,000 |
| 17 | OH | H | H | Cl | H | H | 1/300,000 |

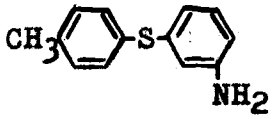
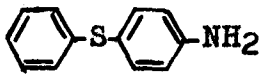
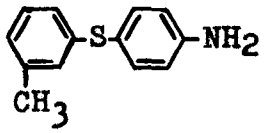
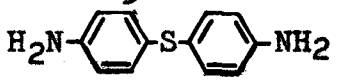
Table III

Antituberculous Activity of Some Dibenzofuran, Dibenzothiophene and Diphenyl Sulfide Derivatives

| No. | Compound | Molar x $10^5$ | Bacteriostatic concentration | |
|---|---|---|---|---|
| | | | mg./100 cc. | mg./100 cc. in presence of 10% serum |
| 1 |  | 0.21 | 0.039 | 5.0 |
| 2 |  | 0.36 | 0.078 | 10 |
| 3 |  | >38 | >10 | >10 |
| 4 |  | 0.60 | 0.16 | >10 |
| 5 |  | 1.2 | 0.31 | >10 |
| 6 |  | 0.2 | 0.039 | 10 |
| 7 |  | 0.2 | 0.039 | 5.0 |
| 8 |  | 0.40 | 0.078 | >10 |
| 9 |  | 1.5 | 0.31 | 10 |

(Continued on next page)

Table III (Continued)

| No. | Compound | Molar x $10^5$ | Bacteriostatic concentration | |
|---|---|---|---|---|
| | | | mg./100 cc. | mg./100 cc. in presence of 10% serum |
| 10 |  | 1.2 | 2.5 | 10 |
| 11 |  | 0.78 | 0.16 | 5.0 |
| 12 |  | 1.5 | 0.31 | 10 |
| 13 |  | 23 | 5.0 | 10 |

diphenyl sulfides from a report by Doub and Youmans;[41] many of the compounds reported in this article were prepared in This Laboratory.

From these results it will be noted that the 2- and 4-aminodibenzofurans are of the same order of activity, the 4- derivative being slightly more active. Bromo-substitution in the same ring as the amino group results in a considerable loss of activity. It is interesting to note that the 2-bromo-3-aminodibenzofuran is 60 fold more active than the 2-amino-3-bromo analog. The monoaminodibenzothiophenes are of

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[41] L. Doub and G. P. Youmans, Am. Rev. Tuberc., 61, 407 (1950).

the same order of effectiveness as the aminodibenzofurans, the 3- and 4-aminodibenzothiophenes showing somewhat greater activity than the 2-amino derivative.

Among the diphenyl sulfides it is noteworthy that the para amino derivative is eight times as active as the ortho isomer. It is also of interest that p-aminodiphenyl sulfide is about 60 times more active than the p,p'-diaminodiphenyl sulfide.

Considerable work has also been reported concerning aryl alkyl ethers and heterocyclic alkyl ethers. A good review of these reports can be found in the discussion of acid-fast infections by Burger.[39]

Most of the ethers and sulfides either lose their effectiveness in vivo or have been proven too toxic to be effective antituberculous agents. They have been stressed here primarily because of their direct relation to the study described in this dissertation.

It is to be expected that antioxidants such as diphenylamine will inhibit the vital oxidative processes of the tubercle bacilli; however, other basic compounds exhibit a similar action, especially the basic dyes. In 1912 Dewitt demonstrated that methylene blue penetrated the bacillus; in both tuberculosis and malaria, methylene blue has shown some activity. The basic dyes are reported[42] to precipitate

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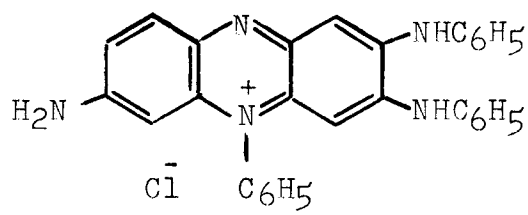
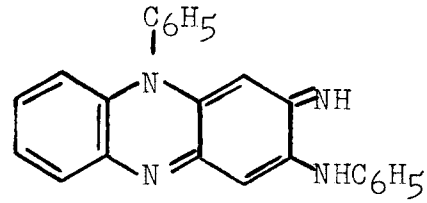
[42] G. Meissner and E. Hesse, Arch. Exptl. Path. Pharmakol., 147, 339 (1930).

the negatively charged bacillary cells by a colloidal process. Two of the most active of the basic dyes are Indamene Blue Extra (IV)[43] and 2-aniline-3-imino-5-phenyl phenazine (V)[44]; the latter compound inhibits the growth of the tubercle bacilli at a concentration of 1/1,000,000.



IV



V

In 1940, in connection with studies of the mode of action of the sulfa drugs, Woods and Fildes[45] discovered that sulfanilamide was completely vitiated by small amounts of p-aminobenzoic acid (PABA). These authors advanced the theory that the sulfa drugs, being structurally similar to the essential metabolite PABA, were absorbed in preference to the essential vitamin thus "starving" the organism. Bell and Roblin[46] in 1942 were able to experimentally confirm this theory.

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[43] M. I. Smith, J. Pharmacol. Exptl. Therap., 20, 419 (1923).

[44] V. C. Barry, J. G. Belton, M. L. Conalty and D. Twomey, Nature, 162, 622 (1948).

[45] D. D. Woods and P. Fildes, Chemistry and Industry, 18, 133 (1940).

[46] P. H. Bell and R. O. Roblin, Jr., J. Am. Chem. Soc., 64, 2905 (1942).

p-Aminobenzoic acid has been shown to be a metabolite of the tubercle bacillus; thus following the announcement of Woods and Fildes, a large volume of antituberculous research has been directed toward metabolite antagonists. In fact, until the discovery of streptomycin this approach showed the greatest possibilities for an effective antituberculous agent. A very good review up to 1946 of the field of metabolite antagonists may be found in the discussion of Broadbent;[16] thus only the more important of the drugs prior to that date will be here mentioned.

As is the case with so many of the new "wonder drugs" the chemotherapeutic ability of the sulfa drugs was at first overrated. Of the sulfanilamide series only sulfathiazole was shown to possess slight tuberculostatic properties. A large amount of research followed with the preparation of many sulfanilamide derivatives for tuberculostatic testing, especially derivatives containing lipid-solubilizing groups; however, none of these compounds has evolved as a practical antituberculous agent.

Levaditi and Pérault[47] were the first to observe that the antibacterial action of p-aminophenyl sulfones was reversed by PABA. 4,4'-Diaminodiphenyl sulfone was shown to possess high antituberculous activity, but proved too toxic

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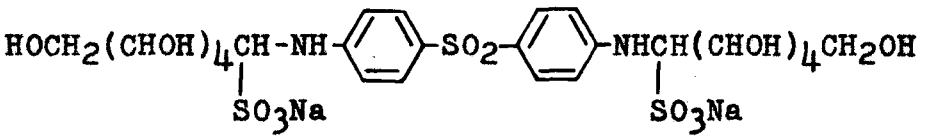
[47] C. Levaditi and R. Pérault, Compt. rend. soc. biol., 139, 1043 (1941).

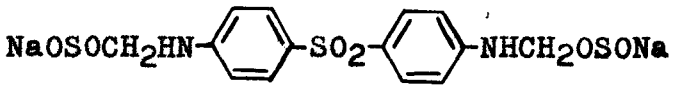
to be used clinically. A number of derivatives of this sulfone has subsequently been prepared with a view toward decreased toxicity with retained activity; these attempts have met with limited success.

The first (1940) of the series was Promin, sodium bis-(4-N-dextrosesulfonate-aminophenyl) sulfone[48] (VI).

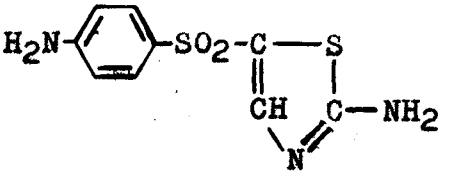


VI

Two other of the early drugs have received considerable attention: Diasone, sodium bis-(4-N-formaldehyde sulfoxylate-aminophenyl) sulfone[49] (VII), synthesized by Raiziss in 1943 and Promizole, 4-aminophenyl-(2-amino-5-thiazolyl) sulfone[50] (VIII), whose preparation was reported by Bambas in 1945.



VII



VIII

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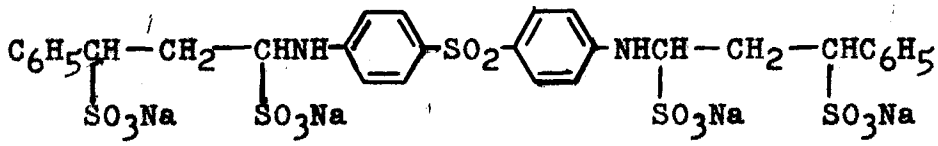
[48] W. H. Feldman, H. C. Hinshaw and H. E. Moses, Proc. Mayo Clin., 15, 695 (1940).

[49] G. W. Raiziss, L. W. Clemence and M. Freifelder, J. Am. Pharm. Assoc., 33, 42 (1944).

[50] L. L. Bambas, J. Am. Chem. Soc., 67, 668 (1945).

The one significant drug of this type which has been reported since 1946 is Sulphetrone, sodium bis-[4-N-3-phenyl-propane-1,3-disulfonate)aminophenyl] sulfone[51] (IX), which has received much attention in England.



IX

In 1943, the isolation of tuberculostearic acid (10-methyl-stearic acid) and phthioic acid (ethyldecyldodecylacetic acid) from the esters produced by the tubercle bacilli was reported.[52] This report and the close relation of the leprosy bacillus to the tubercle bacillus stimulated the testing of many fatty acids. A good review to 1946 of this method of approach may be found in the dissertation of Massie;[17] the material here included is intended to supplement this review.

In 1947, Barry and Twomey[53] reported the synthesis and testing of a rather large series of succinic acids, esters

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[51] W. H. Gray and T. A. Henry, British Patent 491,265 [C. A., 33, 1104 (1939)].

[52] N. Polgar and R. Robinson, J. Chem. Soc., 615 (1943).

[53] V. C. Barry and D. Twomey, Proc. Royal Irish Acad., 51, 152 (1947).

and amides. The most effective compounds *in vitro* were: the n-tetradecyl-, the α-methyl-α'-dodecyl- (and its half esters), the α,α'-diheptyl-, and the p-aminobenzenesulfonamido-succinic acids. Due to high toxicity and lowered activity *in vivo* these compounds have not been employed clinically.

The attachment of fatty acid side chains to heterocyclic rings, such as pyridyl,[54], piperidyl,[54] thiazolyl,[54] quinolyl,[55] and acridyl[55] failed to result in effective antituberculous compounds.

It has been postulated[56] that bacteriostasis by the fatty acids and their derivatives is due to their surface activity and, indeed, in many cases these two properties were found to be proportional. However, several exceptions to this generalization have become evident and have cast considerable doubt upon this theory. If the effectiveness were due primarily to surface activity, highly surface active agents should possess antituberculous activity, while it has been shown that detergents of the polyethylene

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[54] F. Brody and M. T. Bogert, J. Am. Chem. Soc., 65, 1075 (1943).

[55] E. Graef, J. M. Fredericksen and A. Burger, J. Org. Chem., 11, 257 (1946).

[56] W. M. Stanley, G. H. Coleman, C. M. Greer, J. Sacks and R. Adams, J. Pharmacol. Exptl. Therap., 45, 121 (1932).

glycol type actually promote the spread of tuberculosis infections *in vivo*.[39]

Results of the fatty-acid, lipid-soluble approach to the chemotherapy of tuberculosis have been discouraging and almost no reports of importance have appeared in the last few years.

Another interesting group of active tuberculostatic agents is that of the thiosemicarbazones. As was mentioned previously, sulfathiazole has been the only important sulfa drug to exhibit antituberculous activity. Behnisch[57] became interested in this anomaly and investigated the necessity of the thiazole ring for activity and found that sulfanilamidothiadiazole was also effective. A series of sulfathiazoles was prepared and found to be of little value; however, in view of the close structural relationship, the thiosemicarbazones prepared as intermediates for the sulfathiadiazoles were subjected to testing by Behnisch and his coworkers and found to be surprisingly active.[58] The most effective of this group was the *p*-acetaminobenzaldehyde thiosemicarbazone (also known as Amithiozone, Tibione, TB 1, Conteben and Myvisone) (X).

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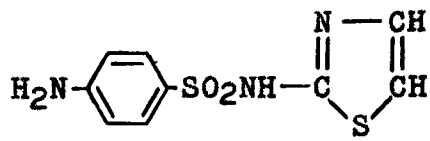
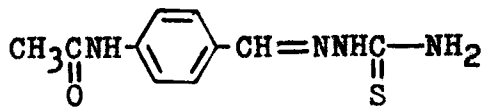
[57] G. Domagk, R. Behnisch, F. Mietzsch and H. Schmidt, Naturwissenschaften, 33, 315 (1946).

[58] R. Behnisch, F. Mietzsch and H. Schmidt, Am. Rev. Tuberc., 61, 1 (1950); R. Behnisch, F. Mietzsch and H. Schmidt, Angew. Chem., 60, 113 (1948).



Sulfathiazole



X
Amithiozone

Amithiozone possesses greater activity than p-aminosalicylic acid (PAS) but is less effective than streptomycin.[59] It has received considerable testing in Europe but because of its toxicity its use has been limited in this country mainly to cases where PAS-resistance has developed.[60] The semicarbazones, oximes, hydrazones, azines and anils of p-acetaminobenzaldehyde do not possess bacteriostatic activity.[58] Shifting of the substituent from *para* to *meta* or *ortho* results in decreased activity. However, activity is retained if the acetamino group is replaced by an ethylsulfenyl, isopropylamino, dimethylamino or similar grouping. The p-ethylsulfonylbenzaldehyde thiosemicarbazone has

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[59] H. H. Fox, J. Chem. Education, 29, 29 (1952).

[60] Report of the American Trudeau Society, Am. Rev. Tuberc., 63, 617 (1951).

received considerable attention in England[61] and possesses activity comparable to Amithiozone.

Quite recently the α-, β- and γ-pyridylaldehyde thiosemicarbazones have been prepared and early tests indicate that the β- and γ- derivatives may be superior to Amithiozone.[59]

The most successful synthetic antituberculous searches to date have been in the field of aromatic and heterocyclic acids and their derivatives. In 1941, Bernheim[62] announced that benzoic acid can be utilized by the tubercle bacillus as its sole source of carbon. This discovery led to the preparation and testing of a large number of substituted benzoic acid derivatives in the hope of finding an effective metabolite antagonist. Many of those acids tested possessing antituberculous activity were iodo and hydroxy substituted derivatives. By far the most successful compound to be evolved from these searches was p-aminosalicylic acid[63] (PAS)(XI).

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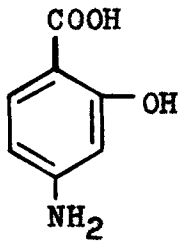
[61] E. A. Hoggarth, R. Martin, N. E. Storey and E. H. P. Young, Brit. J. Pharmacol., 4, 248 (1949); A. R. Martin and G. T. Stewart, Brit. J. Exptl. Path., 31, 189 (1950).

[62] F. Bernheim, J. Bact., 41, 387 (1941).

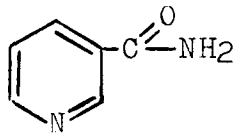
[63] J. Lehmann, Lancet, 250, 14 (1946).




XI
PAS

Though the activity of PAS is considerably less than that of streptomycin, the drug has found extensive application because of its unusually low toxicity. One of the most effective weapons against tuberculosis at the present time is a combination of streptomycin and PAS. It is interesting that PAS seems quite specific in its activity, exerting little bacteriostasis on other pathogenic organisms. Also of interest is the fact that any variation whatsoever in the structure of PAS results in a drastic decrease in activity. Substitution of a chloro or amino group, alkylation of the amino group, and esterification of the carboxyl group all result in a considerable loss of effectiveness. Since PAS is absorbed and excreted quite rapidly it must be administered in large and frequent doses. PAS-resistant strains of the tubercle bacilli may develop, but after cessation of treatment the resistance is soon lost. It is interesting to note that PAS-resistant organisms may be obtained from patients under treatment with this drug although it is quite difficult to produce drug resistance <u>in vitro</u>.

The tuberculostatic action of nicotinamide[64] (XII) is equivalent to that of PAS; however, it has not received such extensive clinical testing because of its greater toxicity. It causes severe liver complications and exhibits strong vasodilator action.



XII

A recent report[65] indicates pyrazinamide (XIII) to be three times as effective as PAS and to possess a similar increase in activity over nicotinamide. A number of other nicotinamide relatives were tested, the only other effective compound being pyridazine-3-carboxamide; this compound is at least as effective as nicotinamide on parenteral administration. Preliminary reports of clinical studies suggest that pyrazinamide is effective in the treatment of patients with tuberculosis; however, tubercle bacilli that are resistant to this drug rapidly appear, thus limiting its period of effectiveness.

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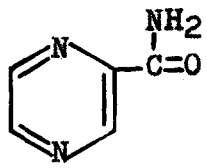
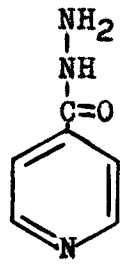
[64] V. Chorine, Compt. rend., 220, 150 (1945); D. McKenzie, L. Malone, S. Kushner, J. J. Oleson and Y. Subbarow, J. Lab. Clin. Med., 33, 1249 (1948).

[65] E. F. Rogers, W. J. Leanza, H. J. Becker, A. R. Matzuk, R. C. O'Neill, A. J. Basso, G. A. Stein, M. Solotorovsky, F. J. Gregory and K. Pfister, Science, 116, 253 (1952).

In the past few months, considerable attention has been directed toward hydrazine derivatives of isonicotinic acid. The two most promising members of this group are isonicotinic acid hydrazide [66,67] (XIV) and 1-isonicotinyl-2-isopropyl hydrazine[67] (XV).



XIII
Pyrazinamide
"Aldinamide" (Lederle)



XIV

Isonicotinic Acid Hydrazide
Isoniazid
"Nydrazid" (Squibb)
"Rimifon" (Hoffmann-LaRoche)
"Ditubin" (Schering)
"Pyricidin" (Nepera)
"Cotinazin" (Pfizer)
"Dinacrin" (Winthrop-Stearns)

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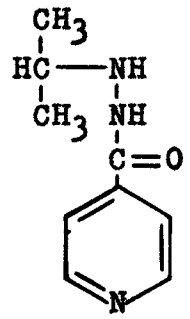
[66] J. Bernstein, W. A. Lott, B. A. Steinberg and H. L. Yale, Am. Rev. Tuberc., 65, 357 (1952).

[67] W. Steenken, Jr. and E. Wolinsky, ibid., 65, 365 (1952).



XV
1-Isonicotinyl-2-isopropyl Hydrazine
"Marsilid" (Hoffmann-LaRoche).

Isonicotinic acid hydrazide (INAH) is bacteriostatic in vitro against M. tuberculosis in a concentration as low as 0.02-0.06 γ per ml. It apparently is rather specific in action, being ineffective against the common gram-positive and gram-negative bacteria, against certain protozoa, and against the influenza virus. From the limited observations available, INAH appears to have approximately the same activity as streptomycin, though one report concerning in vivo testing with mice indicates INAH to be considerably more effective than this antibiotic.[66] From the information available it appears that INAH and its isopropyl derivative (IPH) are of relative low toxicity in dosage ranges. Tubercle bacilli resistant to both of these drugs appear rapidly in vitro and in patients.[68] These two drugs are absorbed rapidly and within an hour after administration

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[68] Report of the American Trudeau Society, Am. Rev. Tuberc., 66, 251 (1952).

appear well distributed throughout the body; the drugs are excreted in the urine.

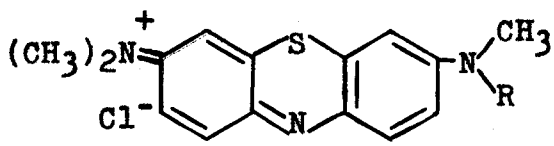
It must be emphasized that the clinical investigations so far are too limited to give an accurate and complete evaluation of these new drugs. A report[68] of the American Trudeau Society in August, 1952, contains the following statement:

> There is no reason to believe that isoniazid and its isopropyl derivative will replace the combination of streptomycin and PAS in the treatment of tuberculosis. It seems more likely that these new drugs will be most valuable in the treatment of patients with strains of tubercle bacilli highly resistant to streptomycin. In such cases, PAS probably should be given also in an effort to prevent the emergence of isoniazid-resistant strains of tubercle bacilli although the efficacy of this combination has not yet been proved.

## Dialkylaminoalkylamines of Fused Heterocyclic Systems

Reports concerning dialkylamines are distributed among almost all of the fields of chemotherapy, the greatest volume appearing in the field of antimalarial research probably because of a larger number of reports in this sphere of activity. Interest in dialkylaminoalkylamines dates back to 1891 when Ehrlich, a pioneer of modern chemotherapy, showed that methylene blue exhibited some antimalarial activity. Based upon this information, the German

investigators Schülemann, Schönhofer and Wingler[69] soon after World War I began their search for synthetic antimalarial drugs. Several modifications of methylene blue (XVI) were investigated and two such derivatives were found to possess considerably enhanced activity (XVII and XVIII).



XVI R = $CH_3-$
XVII R = $(C_2H_5)_2NCH_2CH_2-$
XVIII R = $(C_2H_5)_2NCH_2CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}H-$

The use of cocaine as a local anesthetic dates back to Koller in 1884.[70] In 1890, Ritsert[71] demonstrated that ethyl p-aminobenzoate possessed anesthetic activity. Einhorn, who had worked with Willstätter on the chemistry of cocaine, combined the knowledge obtained from the degredation of cocaine, and the activity of the alkyl p-aminobenzoates to prepare a series of dialkylaminoalkyl esters of aromatic acids. The most important of this series, reported

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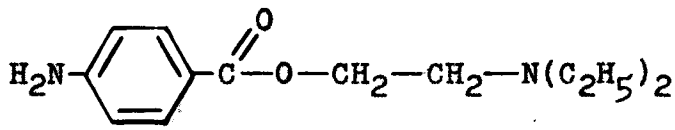
[69] F. Schönhofer, Med. u. Chem., 3, 62 (1938).

[70] G. L. Jenkins and W. H. Hartung, "The Chemistry of Organic Medicinal Products", 3rd ed., John Wiley & Sons, Inc., New York, N. Y., 1949, p. 343.

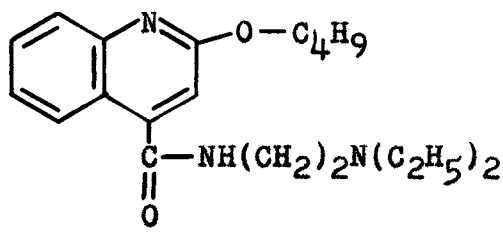
[71] K. Bodendorf, Deut. Apoth. Ztg., 49, 1642 (1934).

in 1909,[72] was procaine (XIX) (whose monohydrochloride is called novocaine).



XIX

Many compounds of related structure have been prepared and found to possess local anesthetic activity; one of the most important of these is nupercaine[73] (XX), a dialkylaminoalkyl amide and a quinoline derivative.



XX

In the field of disinfectants, it has been shown that many of the active compounds owe their bactericidal activity to their initial action as surface-active agents.[74] In 1929, Hartmann and Kaegi[75] reported the preparation of a series of

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[72] A. Einhorn and E. Uhlfelder, Ann., 371, 131 (1909).

[73] K. Miescher, Helv. Chim. Acta, 15, 189 (1932).

[74] A. Burger, "Medicinal Chemistry", Interscience Publishers, Inc., New York, N. Y., 1951, Vol. 2, p. 981.

[75] M. Hartmann and H. Kägi, Z. angew. Chem., 41, 127 (1928).

dialkylaminoalkyl amides of fatty acids which exhibited considerable bactericidal activity; these were of the general formula XXI, where R represents an alkyl group of hydrogen.

$$C_nH_{2n+1}CONRCH_2CH_2N(C_2H_5)_2$$

XXI

In 1935, Domagk[76] reported the bactericidal activity of dodecyldimethylbenzylammonium chloride. The bactericidal activity of benzylalkyldimethylammonium halides, $[C_6H_5CH_2NR(CH_3)_2]\ Cl^-$, increases up to 14 to 16 carbon atoms in the alkyl group with a corresponding increase in surface-active properties.[77] An increasing number of bactericidal cationic detergents have since been prepared in which the dialkylamineakyl group has been replaced by other groupings.[78]

As was pointed out in the initial portion of this section, a vast number of dialkylaminoalkylamines have been tested for anti-malarial properties; only the most important of these will be briefly considered here. A complete coverage of antimalarial research in this country from

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[76] G. Domagk, Deut. med. Wochschr., 61, 829 (1935).

[77] E. I. Valko and A. S. DuCois, J. Bact., 50, 481 (1945).

[78] H. R. Ing in H. Gilman, "Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1953, Vol. 3.

1941-1945 is available in a survey by Wiselogle;[79] a review of acridine derivatives through 1950 is also available.[80]

Research based upon the antimalarial activity shown by methylene blue derivatives produced (in 1924) the first useful synthetic compound, pamaquine (or plasmochin)[81] (XXII). Extension of this line of research led to the preparation (in 1934) and testing of quinacrine (or atabrine)[82] (XXIII). Of the thousands of compounds tested during World War II the following are of particular importance: chloroquine (aralen)[83](XXIV), amodiaquin (Camoquin)[84] (XXV), pentaquine(XXVIa),[85] isopentaquine[86] (XXVIb), primaquine[86] (XXVIc) and chloroguanide (Pauludrine)[87] (XXVII).

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[79] "Survey of Antimalarial Drugs, 1941-1945", edited by F. Y. Wiselogle, Edwards Brothers, Inc., Ann Arbor, Mich., 1946.

[80] A. Albert, "The Acridines, Their Preparation, Physical, Chemical and Biological Properties and Uses", Arnold, London, 1951.

[81] W. Schulemann, F. Schönhöfer and A. Wingler, German Patent 486,079 [Chem. Zentr., 101, 1006 (1930)].

[82] F. Mietzch and H. Mauss, Angew. Chem., 47, 633 (1934).

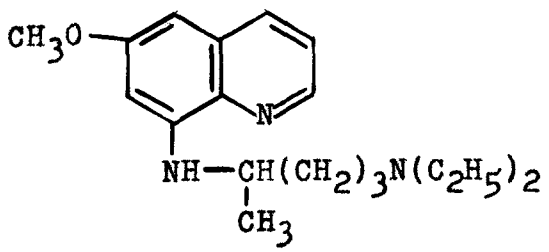
[83] H. Andersag, S. Breitner and H. Jung, U. S. Patent 2,233,970 [C. A., 35, 3771 (1941)].

[84] J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb and A. L. Rawlins, J. Am. Chem. Soc., 70, 1363 (1948).

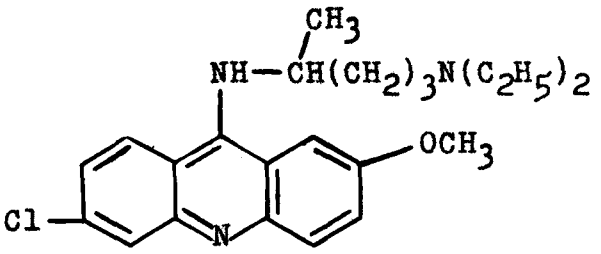
[85] N. D. Drake, J. Van Hook, J. A. Garman, R. Heyes, R. Johnson, G. W. Kelley, S. Melamed and R. M. Peck, ibid., 68, 1529 (1946).

[86] R. C. Elderfield et al., ibid., 68, 1524 (1946).

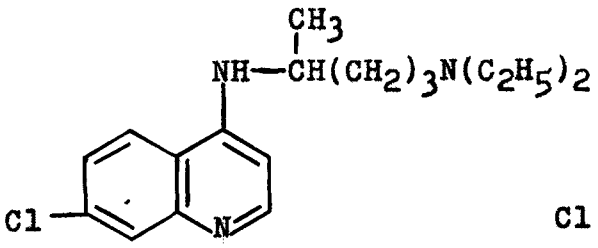
[87] F. H. S. Curd, D. G. Davey and F. L. Rose, Ann. Trop. Med., 39, 139 (1945).



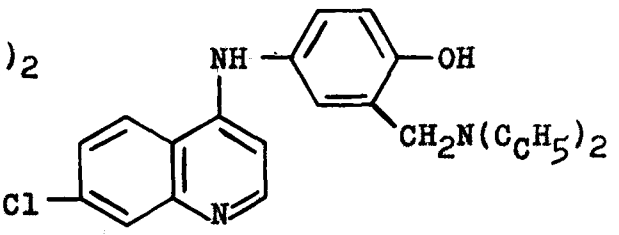
XXII Pamaquine



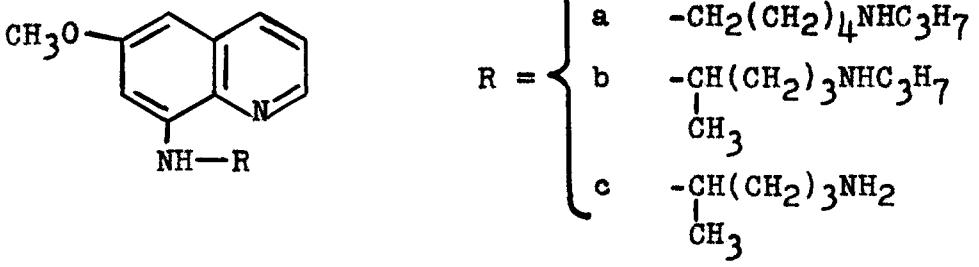
XXIII Quinacrine



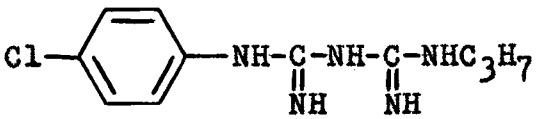
XXIV Chloroquine



XXV Amodiaquin

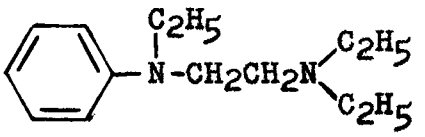


XXVI



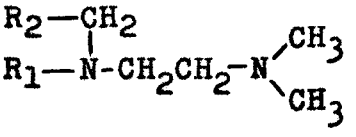
XXVII Chloroguanide

The most recent field of extensive research concerning dialkylaminoalkylamines is that of the antihistaminics. The first compound of this type that was shown to possess antihistaminic activity was Fourneau's compound F-1571 (XXVIII).[88]



XXVIII

This compound proved too toxic for clinical testing, but investigations of structural variations have been quite fruitful. Since 1940, the testing of a constantly increasing number of compounds has been reported. Many of the presently important compounds are quite similar in structure:



XXIX

a $R_1 = R_2$ = phenyl (Antergan)

b $R_1$ = phenyl; $R_2$ = 2-thienyl (Diatrin)

c $R_1$ = 2-pyridyl; $R_2$ = phenyl (Pyribenzamine)

d $R_1$ = 2-pyrimidyl; $R_2$ = p-methoxyphenyl (Neohetramine)

e $R_1$ = 2-pyridyl; $R_2$ = p-methoxyphenyl (Neoantergan)

f $R_1$ = 2-pyridyl; $R_2$ = 2-thienyl (Histadyl)

g $R_1$ = 2-pyridyl; $R_2$ = 5-chloro-2-thienyl (Clorothen)

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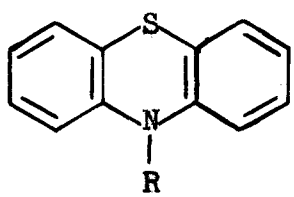
[88] G. J. Jenkins and W. H. Hartung, "The Chemistry of Organic Medicinal Products", 3rd ed., John Wiley & Sons, Inc., New York, N. Y., 1949, p. 333.

Another series of compounds which proved to be very effective antihistaminic substances is the 10-dialkylaminoalkylphenothiazines. The compound which first attracted attention to this series, the 10-p-diethylaminoethylphenothiazine (XXXa) was first synthesized for antimalarial testing in This Laboratory.[89] The most active of this series is the dimethylaminoisopropyl analog[90,91] (XXXb) which is reported to be fifteen times as active as Pyribenzamine and its duration of action was three times as long when tested against doses of histamine in guinea pigs.



a R = $(C_2H_5)_2NCH_2CH_2-$

b R = $(CH_3)_2N-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-$

XXX

The discussion of dialkylaminoalkylamines thus far has been admittedly brief, including only some of the most important compounds. The remainder of this section will be directed to correlations of structure and physiological activity.

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[89] H. Gilman and D. A. Shirley, J. Am. Chem. Soc., 66, 888 (1944).

[90] B. N. Halpern, J. Am. Med. Assoc., 129, 1219 (1945).

[91] B. N. Halpern and R. Ducrot, Compt. rend. soc. biol., 140, 361 (1946).

> "In the chemistry of the organic dyestuffs the conception of the chromophore and the auxochrome group is valid throughout the whole field, connecting colour and constitution. Light absorbing groupings, the recognition of many of which is now classical, e.g., the azo group, will always produce colour, and the nature of the colour is modified by parts of the molecule other than the chromophoric group proper. There is no widely applicable analogy in the case of biological activity although certain groupings may be associated with activities of varying kinds. The presence of the particular grouping, however, is not always a guarantee of biological activity; consequently it is dangerous to generalize, and apparently anomalous results are common. Activity must be considered as a function of the molecule as a whole."[92]

A discussion of the heterocyclic dialkylaminoalkylamines may be divided into three categories: the amino group, the alkyl chain and the heterocyclic substituent. It must be emphasized that the generalizations which follow are not without their exceptions.

As to the degree of substitution of the amino group, primary amines are usually more active than the secondary amines and the latter more effective than tertiary amines. Burger[93] in a general discussion reports that primary amines usually are the more toxic while Jenkins and Hartung in a

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[92] W. A. Sexton, "Chemical Constitution and Biological Activity", E. & F. N. Spon Ltd., London, 1949, p. 85.

[93] A. Burger, "Medicinal Chemistry", Interscience Publishers, Inc., New York, N. Y., 1951, Vol. 1, p. 32.

similar discussion[94] state that the primary amines are generally the less toxic. Substitution of the chain amine usually results in a marked increase in activity as is exemplified by the antihistaminics.

Considering the terminal nitrogen, the most active compounds contain a dimethylamino grouping; this seems especially true with antihistaminic compounds. Diethyl or higher homologs are generally less active and exhibit increased toxicity. Cyclic amino groups such as pyrrolidine, piperidine, morpholine, thiomorpholine or 2-imidazolinyl may be substituted without serious loss of activity; however, substitutions on the pyrrolidine ring result in a decreased activity.[95] The replacement of the dimethylamino group by an unsymmetrically substituted amino group has resulted in a decrease in activity in the few known examples.[95]

Apparently, for greatest effectiveness, the amino groups should preferably be symmetrically substituted, small and planar. An approximate order of decreasing utility of the various groups is the following:

$$(CH_3)_2N \geq C_4H_8N = C_5H_{10}N > C_4H_8N > C_4H_8ON = C_4H_8SN > (C_2H_5)_2N > (C_4H_9)_2N > NHR > NH_2$$

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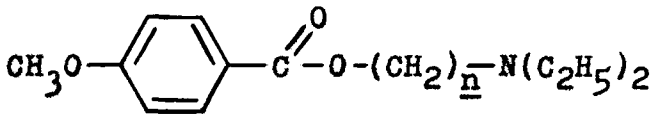
[94] G. L. Jenkins and W. H. Hartung, "The Chemistry of Organic Medicinal Products", 3rd ed., John Wiley & Sons, Inc., New York, N. Y., 1949, p. 351.

[95] F. Leonard and C. P. Huttrer, "Histamine Antagonists", National Research Council, Washington, D. C., 1950, p. 23.

General statements about variations in the alkyl side chain are especially difficult. For example, p-methoxyphenylcarbamide is tasteless, while the ethoxy analog is 200 times as sweet as sugar. 10-β-Dimethylaminoisopropylphenothiazine has an antihistaminic activity 75 fold greater than the 10-β-dimethylaminoethyl derivative. Also, certain dyes containing the diethylamino group dye nerve fiber while the very similar dimethylamino compounds do not have this ability.

The optimum chain length depends upon the type of compound to be tested. For antihistaminic compounds the preferred chain length is two carbon atoms, and activity drops off rapidly with further lengthening of the chain. For antimalarials a four-carbon chain usually shows the greatest activity. Studies with anesthetics of the type



have shown the compound in which n was 3 to be six times more effective than the ester in which n was 2; a maximum activity was reached when n was 5.[96] However, if the methoxyl group was replaced by an amino group, a maximum activity was reached when n was 2 or 3.

Again when considering the effect of branching the

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[96] C. Rohmann and B. Scheurle, Arch. Pharm., 274, 110 (1936).

chain conflicting reports are obtained. With anesthetics, normal alkyl compounds are more effective than their branched analogs. With antimalarials, branching of the chain usually results in decreased activity except for an α-methyl group; the principal effect of introducing an α-methyl group is a lowering of the toxicity. The fact that Phenergan is 75 times more effective as an antihistaminic than its dimethylaminoethyl analog has been mentioned. A number of compounds in which the ethylenediamine group has been replaced by the piperazine ring have been found to be antihistaminically active.[97]

The final consideration is that of the heterocyclic system. Dialkylaminoalkylamines of most of the common heterocycles have been prepared and many have been found to be chemotherapeutically useful.

Of the five-membered rings with one hetero atom the derivatives of dibenzofuran and dibenzothiophene are of particular interest in view of the topic of this dissertation. A series of dialkylaminoalkylamino compounds has been prepared in this laboratory[12,98] including the 2-, 3- and

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[97] K. E. Hamlin, A. W. Weston, F. E. Fischer and R. J. Michaels, Jr., J. Am. Chem. Soc., 71, 2731 (1949); R. Baltzly, S. Dubreuil, W. S. Ide and E. Lorz, J. Org. Chem., 14, 775 (1949).

[98] H. Gilman and S. Avakian, J. Am. Chem. Soc., 68, 580 (1946).

4-γ-diethylaminopropylamino-, the 3-γ-diethylaminopropylamino-6-iodo-, the 2,7- and 2,8-bis-(γ-diethylaminopropylamino)-, the 3-γ-diethylaminopropylamino-2- (and 4-)-methoxy-, the 2-γ-diethylaminopropyl-3-bromo-, the 1-bromo-3-γ-diethylaminopropylamino-4-methoxy-, the 1-γ-diethylaminopropylamino-3,4-dimethoxy-dibenzofurans and the 2- and 4-γ-diethylaminopropylamino-, the 2-γ-diethylaminopropylamino-3-chloro (and bromo)- and the 1-γ-diethylaminopropylamino-4-methoxydibenzothiophenes. Also, a series of N-dialkylaminoalkylcarbazoles has been prepared and tested for antihistaminic properties.[99]

Among the six-membered rings containing one hetero atom, quinoline antimalarials such as plasmoquin, chloroquin and camoquin have already been mentioned, as has the acridine derivative atebrine. 1-(Diethylaminoethylamino)-4-methylthioxanthone (Miracil D) has recently been shown[100] active against schistomiasis.

The antihistaminic properties of phenothiazine (a six-membered heterocycle with two hetero atoms) derivatives have been discussed. Also of interest among this group are the

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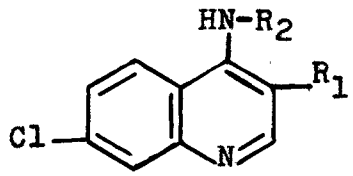
[99] F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. A. Weisel and W. H. Yanko, ibid., 66, 725 (1944).

[100] H. Mauss, Chem. Ber., 81, 19 (1948).

2-dialkylaminoalkylaminophendioxins[101] and the antimalarial compound of 1-diethylaminopropylaminophenoxathiin.[79]

Finally, brief mention should be made of the effect of other nuclear substituents upon activity. For example, the considerable activity of 1-(diethylaminoethylamino)-4-methylthioxanthone against schistomiasis has just been mentioned; however, the replacement of the methyl group by a hydrogen atom completely abolishes the activity.[102] The 4-diethylaminopropylamino-6-methoxyquinoline possesses high antimalarial activity while the 2-diethylaminopropylamino-6-methoxy analog is inactive.[102] A study of variations of antimalarial compounds of the type




reveals that any change of the position of the chloride atom greatly decreases the effectiveness; also, in this case, chlorine was shown to be more effective than the other halogens. If $R_1$ was $CH_3$ rather than H, a more active compound was obtained.

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[101] M. Tomita, J. Pharm. Soc. Japan, 56, 829 (1936) [C.A., 32, 8427 (1938)].

[102] W. H. Powers, "Chemotherapy", Reinhold Publishing Corp., New York, N. Y., 1946, pp. 65-67.

Little generalization can be made concerning the effect of nuclear substituents upon physiological activity as a whole; it is necessary to consider each type of compound and the type of activity for which it is to be tested. This brief review of some of the more important compounds attests to the considerable importance of the heterocyclic dialkylaminoalkylamines. The current fervor, particularly with respect to antihistaminic substances, indicates that the future of this field of study will be far from stagnant.

## Derivatives of Dibenzofuran and Dibenzothiophene

Table IV is an extension of the compilation of known derivatives of dibenzofuran listed by Swislowsky,[7] Cheney,[6] Willis,[8] and Hogg.[10] In the Table are entered all dibenzofuran derivatives with the appropriate references which were not included in the earlier tabulations. In Table IV, the literature was covered thoroughly through 1950. The additional dibenzofuran derivatives in Table V appear in a separate table since the 1951 Index to Chemical Abstracts was not available until after the principal portion of this thesis had been written and typed. Table V covers the literature from 1950-1951. Table VI is an extension of the compilation of known derivatives of dibenzothiophene prepared by Nobis[13] and Esmay,[14] and covers the literature from 1950-1951.

Table IV

Derivatives of Dibenzofuran

| Name of Compound | M.P. | Reference |
|---|---|---|
| MONOSUBSTITUTED DIBENZOFURANS | | |
| 1-Acetaminodibenzofuran | 205 | (103) |
| 2-Acetaminodibenzofuran | 161-2 | (7),p.104 |
| | 166-166.5 | (103) |
| 3-Acetaminodibenzofuran | 177-8 | (104,105,106 107) |
| | 182 | (103) |
| | 183 | (108) |
| 4-Acetaminodibenzofuran | --- | (109) |
| | 235-6 | (103) |

(Continued on next page)

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103 S. Yamashiro, Bull. Chem. Soc. Japan, 16, 61 (1941)

104 H. Gilman, G. E. Brown, W. G. Bywater and W. H. Kirkpatrick, J. Am. Chem. Soc., 56, 2473 (1934).

105 P. T. Parker, Doctoral Dissertation, Iowa State College, 1936.

106 E. Eagle and A. J. Carlson, J. Pharmacol. Exptl. Therap., 99, 450 (1950).

107 E. C. Miller, J. A. Miller, R. B. Sandin and R. K. Brown, Cancer Research, 9, 504 (1949).

108 R. Adams, J. H. Clark, N. Kornblum and H. Wolff, J. Am. Chem. Soc., 66, 22 (1944).

109 H. Gilman and J. Swiss, J. Am. Chem. Soc., 66, 1884 (1944).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 7-Acetamino-1,2,3,4-tetrahydrodibenzofuran | 146 | (110),p.103 |
| 2-Acetoxydibenzofuran | 115-6<br>118-9 | (7),p.70<br>(111) |
| 4-Acetoxydibenzofuran | 99-100 | (112) |
| 4-Acetoxymercuridibenzofuran | --- | (113) |

(Continued on next page)

110 W. H. Kirkpatrick, Doctoral Dissertation, Iowa State College, 1935.

111 K. Schimmelschmidt, Ann., 566, 184 (1950).

112 T. H. Cook, Doctoral Dissertation, Iowa State College, 1940.

113 C. Handley, N. M. Phatak and C. M. Leake, Univ. Calif., Pub. Pharmacol., 1, 175 (1939) [C.A., 33, 8802 (1939)].

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Acetyldibenzofuran | --- | (110),p.89, (114,115,116, 117,118,119) |
| | 80-1 | (120,121) |
| 3-Acetyldibenzofuran | 120-2 | (119) |
| 2-Acetyldibenzofuran picrate | 81-3 | (115,116) |
| 3-$N^2$-Acetylsulfanilamidodibenzofuran | 223-4 | (8),p.58 (122) |
| 3-$N^4$-Acetylsulfanilamidodibenzofuran | 246-7 | (123,124) |

(Continued on next page)

114 U. S. Patent 2,500,734 [C. A., 44, 5390 (1950)].

115 U. S. Patent 2,498,473 [C. A., 44, 6439 (1950)].

116 British Patent 633,151 [C. A., 44, 5914 (1950)].

117 E. A. Kern and C. W. Wilson, Chem. Eng., 55, 114 (1948).

118 H. Gilman and S. Avakian, J. Am. Chem. Soc., 68, 2104 (1946).

119 H. Gilman, P. T. Parker, J. C. Bailie and J. C. Brown, ibid., 61, 2836 (1939).

120 Ng. Ph. Buu-Hoï and R. Royer, Rec. trav. chim., 67 175 (1948).

121 N. B. Eddy, J. Pharmacol., 58, 159 (1936).

122 H. B. Willis, Iowa State Coll. J. Sci., 18, 98 (1943).

123 C. Tani and H. Ohsaka, J. Pharm. Soc. Japan, 70, 126 (1950).

124 A. Novelli, Ciencia, 1, 260 (1940) [C. A., 34, 7903 (1940)].

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 4-$N^2$-Acetylsulfanilamidodibenzofuran | 218 | (8),p.59<br>(122) |
| 2-Allyloxydibenzofuran | b.p.,178-180/ 4 mm. | (125) |
| 1-Aminodibenzofuran | 113.5-4.5 | (103) |
| 2-Aminodibenzofuran | ---<br>125-6<br>129-130<br>125-25.5 | (9,126,122)<br>(7),p.103<br>(111)<br>(103 |
| 3-Aminodibenzofuran | 95-6<br>99<br>93-94<br>---<br>98 | (12),p.35<br>(103)<br>(127)<br>(37,123,128, 126,98,129)<br>(121) |
| 4-Aminodibenzofuran | 81-2<br>84-5<br><br>118-9 | (130,8)<br>(12,10,122, 109,129)<br>(103) |

(Continued on next page)

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[125] A. L. Jacoby, D. M. Hayes and P. R. Van Ess, Proc. Iowa Acad. Sci., 43, 204 (1936).

[126] U. S. Patent 2,407,704 [C. A., 41, 1458 (1947)].

[127] I. Kh. Fel'dman, J. Gen. Chem. (U. S. S. R.), 6, 1234 (1936) [C. A., 31, 1407 (1937)].

[128] G. A. Martin, Jr., Iowa State Coll. J. Sci., 21, 38 (1946).

[129] H. Gilman and S. Avakian, J. Am. Chem. Soc., 67, 349 (1945).

[130] W. Borsche and B. Schacke, Ber., 56, 2498 (1923).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Aminodibenzofuran hydrochloride | --- | (131,110,8) |
| 3-Aminodibenzofuran hydrochloride | 220 | (1,131,110) |
| 4-Aminodibenzofuran hydrochloride | --- | (1,8) |
| 1-Amino-4-(3-dibenzofurylamino)-anthraquinone-2-carboxylic acid | --- | (126) |
| 1-Amino-4-(2-dibenzofurylamino)-anthraquinone-2-sulfonic acid | --- | (126) |
| 1-Amino-4-(3-dibenzofurylamino)-anthraquinone-2-sulfonic acid | --- | (126) |
| 2-(β-Aminoethyl)-dibenzofuran | b.p.,167-170/ 2 mm. | (8,122) |
| 3-(α-Aminoethyl)-dihydrodibenzofuran hydrochloride | 248 | (132) |
| 6-Amino-1,2,3,4-tetrahydrodibenzofuran | --- | (133) |
| 7-Amino-1,2,3,4-tetrahydrodibenzofuran | 55-6 | (110) |
| 6-Amino-1,2,3,4-tetrahydrodibenzofuran hydrochloride | 228 d. | (133) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 7-Amino-1,2,3,4-tetrahydrodibenzofuran hydrochloride | 269 | (110) |
| 7-Amino-1,2,3,4-tetrahydrodibenzofuran picrate | 187-8 | (110) |
| 3,3'-Azobisdibenzofuran | 268-270 | (9) |
| 3-Benzenesulfonamidodibenzofuran | 162-3 | (108) |
| 3-Benzoylaminodibenzofuran | 201 | (134) |
| N-Benzoyl-2-(β-aminoethyl)-dibenzofuran | 183.5-9.5 | (8) |
| 2-Benzoyldibenzofuran | 135-6 | (122) |
| 2-Benzoyldibenzofuran oxime | 182-3 | (122) |
| Bi-3-dibenzofuryl | 245-6 | (8) |
| 1-Bromodibenzofuran | 64-5 | (10) |
| 2-Bromodibenzofuran | 108-9<br>109-110<br>--- | (12,3,131,98)<br>(110,135)<br>(120,136) |
| 3-Bromodibenzofuran | 118-9<br>119-120<br>121-122 | (131)<br>(7)<br>(135) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 4-Bromodibenzofuran | 72<br>70-1 | (137)<br>(119,138) |
| 2-(β-Bromoethyl)-dibenzofuran | 62-62.5 | (8,110,122) |
| 3-Butyl-2-(2-dibenzofuranyl)-indole | 122 | (138) |
| 2-Butyryldibenzofuran | 65 | (120) |
| 2-Caproyldibenzofuran | 87<br>b.p.,242/<br>16 mm. | (120) |
| 1-Carbomethoxydibenzofuran | 63 | (139) |
| 2-Carbomethoxydibenzofuran | 73-4<br>81<br>82-3 | (132)<br>(140)<br>(121) |
| 3-Carbomethoxydibenzofuran | 138 | (140) |
| 2-( -Chloroacetyl)-dibenzofuran | 109-110<br>b.p.,206-8/<br>1-2 mm. | (110) |
| x-Chlorodibenzofuran | 172-4 | (141) |

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141 E. W. Smith, Doctoral Dissertation, Iowa State College, 1936.

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Chlorodibenzofuran | 102 | (110,141) |
| 2-Chloromercuridibenzofuran | 235 | (136) |
| 4-Chloromercuridibenzofuran | 225-7 | (141) |
| Chloromethyl-2-dibenzofuryl methylcarbinol | b.p.,205-6/ 2 mm. | (110) |
| 2-Cyanodibenzofuran | 137 | (1,131,142) |
| 2-Diacetaminodibenzofuran | 127-8<br>125-8 | (143)<br>(131) |
| Diazomethyl 2-dibenzofuryl ketone | 126-7 | (118) |
| Diazomethyl 4-dibenzofuryl ketone | 72-5 | (144) |
| 2-Dibenzofuranacetamide | 209-210 | (118) |
| 2-Dibenzofuranacetic acid | 162-3 | (145-118) |
| 2-Dibenzofuranacetonitrile | 89-90<br>b.p.,185-190/ 0.1 mm.<br>100-2 | (145,146)<br><br>(118) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Dibenzofuranarsonic acid | 250 | (136) |
| 3-Dibenzofuranarsonic acid | 275 | (136) |
| Dibenzofuranazophenol | 199 | (134) |
| 2-Dibenzofuranbutyric acid | 112-3 | (105,147) |
| 2-Dibenzofurancarboxaldehyde | 71-2 | (141,142) |
| Dibenzofuran-4-aldehyde | b.p.,176-9/ 1 mm. | (148) |
| Dibenzofuran-4-aldehyde, 2,4-dinitrophenylhydrazone | 301-2 | (148,149) |
| 1-Dibenzofurancarboxylic acid | 232 | (10,150) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Dibenzofurancarboxylic acid | 240-2 | (8) |
| | 246 | (1,131,110, 141,140,151, 152,153,154, 155,118) |
| | 248-9 | (132) |
| 3-Dibenzofurancarboxylic acid | --- | (131,156) |
| | 271 | (132) |
| 4-Dibenzofurancarboxylic acid | 204-5 | (7) |
| | 208-210 | (3) |
| | --- | (157,137,158, 159,8,160, 151) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 4-Dibenzofurancarboxylic acid amide | 181-2 | (110) |
| 2-Dibenzofurancarboxylic acid chloride | 103-4 | (118) |
| 4-Dibenzofurancarboxylic acid chloride | --- | (8,131,105, 161) |
| 4-Dibenzofurancarboxylic acid diethylamide | 116.5 | (8) |
| 2-Dibenzofurancarboxylic acid dimethylamide | 77-8 | (122) |
| 4-Dibenzofurancarboxylic acid dimethylamide | 116.5 | (8,122) |
| 2-Dibenzofuran-γ-ketobutyric acid amide | 157 | (162) |
| 2-Dibenzofuran-γ-ketobutyric acid chloride | b.p.,270-2/ 10-12 mm. | (162) |
| Dibenzofuran-2-propionic acid | 127-8 | (120) |
| 2-Dibenzofuransulfonic acid | 147<br>--- | (163)<br>(1,141,164, 165,142) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Dibenzofuransulfonic acid p-toluidide | 232-3 | (141) |
| 2-Dibenzofuransulfonyl chloride | 140 | (141) |
| 2-(2-Dibenzofuranyl)-3-propylindole | 90-2<br>b.p.,325-8/16 mm. | (138) |
| β-Dibenzofuroylacrylic acid | --- | (166) |
| β-2-Dibenzofuroylpropionic acid | 185-6 | (105) |
| 4-Dibenzofurylacetamide | 211-2<br>213-4 | (119)<br>(146) |
| 4-Dibenzofurylacetic acid | 213.5-4.5 | (119) |
| 4-Dibenzofurylacetyl chloride | --- | (105,144) |
| 3-Dibenzofurylammonium α-chloroacetate | --- | (9) |
| 3-Dibenzofurylarsine oxide | 250 | (136) |
| γ-2-Dibenzofurylbutyric acid | 112-3 | (119,105,162) |
| 2-(2-Dibenzofuryl)-cinchoninic acid | 245-6 | (120) |
| 2-Dibenzofuryldichloroarsine | --- | (136) |
| 3-Dibenzofuryldichloroarsine | 130 | (136) |
| 3-Dibenzofurylglycine | 139-142 d. | (9) |

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166 U. S. Patent 2,381,880 [C. A., 39, 5094 (1945)].

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 3-Dibenzofurylglycine methyl ester | 123-4 | (9) |
| 2-Dibenzofurylheptadecyl ketone | 83-4 | (167) |
| 1-(4-Dibenzofuryl)-isoquinoline | 137-8 | (105,144) |
| 1-(4-Dibenzofuryl)-isoquinoline hydrochloride | --- | (105-144) |
| 2-Dibenzofurylmethyl carbinol | ---<br>63-4 | (115,117)<br>(121) |
| 4-Dibenzofuryl-N-piperidino-methane | b.p.,175-180/ 0.5 mm. | (148) |
| 4-Dibenzofuryl-N-piperidino-methane picrate | 177-8 | (148) |
| γ-(2-Dibenzofuryl)-propyl-urethane | 73-4 | (162) |
| 2-(2-Dibenzofuryl)-quinoline | 139 | (120) |
| 2-(2-Dibenzofuryl)-quinoline picrate | 220-1 | (120) |
| 2-Dibenzofurylundecyl ketone | 74-5 | (167) |
| 3-Dibenzofurylurea | 222-3 | (144,119) |
| 3-(3,5-Dibromophenylsulfon-amido)-dibenzofuran | 199-200 | (123) |
| 2-Dichlorophosphinodibenzofuran | b.p.,245-250/ 25 mm. | (168) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| Di-4-Dibenzofuryl ketone | 165-8<br>172-3 | (7)<br>(8) |
| Di-4-dibenzofurylthallium chloride | --- | (169) |
| 2- -Diethylaminoacetyldibenzofuran | --- | (110) |
| 3-Diethylaminodibenzofuran | 68<br>b.p.,205/<br>2-3 mm. | (11,170) |
| 4-Diethylaminodibenzofuran | 68-9 | (160) |
| 3-Diethylaminodibenzofuran hydrochloride | 203-5 | (110) |
| Diethyl 3-aminodibenzofuran-N-ethylmalonate | 99-100 | (8) |
| Diethyl 4-aminodibenzofuran-N-ethylmalonate | 75-6 | (8) |
| 3-(Diethylaminoethoxyethylamino)-dibenzofuran | b.p.,235/<br>1 mm. | (171) |
| 2-α-Diethylaminoethyldibenzofuran | --- | (105,144) |
| β-Diethylaminoethyl-2-dibenzofurancarboxylate hydrochloride | 185 | (152) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| β-Diethylaminoethyl-3-dibenzofurancarboxylate hydrochloride | 221 | (152) |
| β-Diethylaminoethyl-4-dibenzofurancarboxylate hydrochloride | 210 | (152) |
| 2-α-Diethylaminoethyldibenzofuran hydrobromide | --- | (105) |
| 2-α-Diethylaminoethyldibenzofuran hydrochloride | --- | (105) |
| 2-(β-Diethylaminoethyl)-dibenzofuran picrate | 173-4 | (144) |
| 2-[(Diethylaminoethyl)-guanylguanido]-dibenzofuran | 98 | (172) |
| Diethylaminomethyl-2-dibenzofurylmethyl carbinol | --- | (110) |
| Diethylaminomethyl-2-dibenzofurylmethyl carbinol hydrochloride | 145 | (110) |
| 2-[2-(Diethylamino)-1-oxo]-ethyldibenzofuran hydrochloride | 200-211 | (121,173) |
| 2-γ-Diethylaminopropylaminodibenzofuran | b.p.,185-190/ 2 mm. | (12,98) |
| 3-γ-Diethylaminopropylaminodibenzofuran | b.p.,260-1/ 0.5 mm. | (12,98) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 4-γ-Diethylaminopropylamino-dibenzofuran | b.p.,210-3/ 0.5 mm. | (12,98) |
| 1,4-Dihydro-7-acetyldibenzofuran | 117 | (132) |
| 1,4-Dihydro-7-acetyldibenzo-furan oxime | 166 | (132) |
| 1,4-Dihydro-3-aminodibenzofuran | 72 | (174) |
| 1,4-Dihydro-7-α-aminoethyldi-benzofuran hydrochloride | 248 | (132) |
| 1,2-Dihydro-2-dibenzofuran-carboxylic acid | 278-9 | (132) |
| 3,4-Dihydro-2(1H)-dibenzofuranone | 105-6 | (175) |
| 2-[3-(1,4-Dihydro-3-hydroxy-1,4-dioxo-2-naphthyl)-propyl]-di-benzofuran | 154.8-6.8 | (176) |
| 3,4-Dimethoxy-α-(4-dibenzofuryl-acetamino)-acetophenone | 186-7 | (119) |
| 3,4-Dimethoxy-α-(4-dibenzofuroyl-amino)-acetophenone | 178-9 | (119) |
| 3-Dimethylaminodibenzofuran | 96 | (121) |
| 4-Dimethylaminodibenzofuran | 98-9 | (7) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 3-Dimethylaminodibenzofuran hydrochloride | 230-2<br>191-3 | (110)<br>(121) |
| 2-(Dimethylaminomethyl)-dibenzofuran hydrochloride | --- | (177) |
| 2-[2-(Dimethylamino)-1-oxo]-ethyldibenzofuran hydrochloride | 235-7 d. | (121,173) |
| 2-(β-Dimethylaminopropionyl)-dibenzofuran | 88-9 | (144) |
| 2-(β-Dimethylaminopropionyl)-dibenzofuran hydrochloride | 194-5 | (105,144) |
| 1,2-Diphenyl-2-(2-dibenzofuryl)-ethylene | 143<br>b.p.,310-2/10 mm. | (120) |
| Dodecylammonium 2-dibenzofurancarboxylate | 87.5-88.5 | (155) |
| N-Dodecyl 2-dibenzofurancarboxamide | 112-3 | (155) |
| 2-(Diphenylstibino)-dibenzofuran | 125-8 | (178) |
| 3-Ethylaminodibenzofuran | 69-70 | (119) |
| 3-Ethylaminodibenzofuran hydrochloride | 228-229 | (119) |
| 2-[2-(Ethylamino)-1-hydroxy]-ethyldibenzofuran | 99.5-101 | (173) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Ethyldibenzofuran | ---<br>b.p.,170-3/ 11 mm.<br>b.p.,175-180/ 15 mm. | (114,179,180)<br>(116)<br>(181) |
| 3-Ethyl-2-(2-dibenzofuryl)-cinchoninic acid | 301-3 d. | (120) |
| 2-Ethyl-2-(2-dibenzofuryl)-quinoline | 141 | (120) |
| 3-Ethyl-2-(2-dibenzofuryl)-quinoline | 215 d. | (120) |
| Ethyl ether of piperidinomethyl-2-dibenzofurancarbinol hydrochloride | 175 | (110) |
| 3-Ethylnitrosoaminodibenzofuran | 136-7 | (119) |
| 2-Fluorodibenzofuran | 88.5-88.8 | (128) |
| 3-Fluorodibenzofuran | 88.5 | (128) |
| 2-(2-Furoyl)-dibenzofuran | 84<br>b.p.,264-5/ 15 mm. | (120) |
| 3-Guanidodibenzofuran hydrobromide | 142 | (182) |
| 3-(Guanylguanido)-dibenzofuran | 186 | (172) |

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[180] British Patent 635,632 [C. A., 44, 6439 (1950)].

[181] British Patent 635,631 [C. A., 44, 7883 (1950)].

[182] German Patent 632,572 [C. A., 31, 218 (1937)].

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 3-(Guanylmethylguanido)-dibenzofuran | 188 | (172) |
| 1,5a,6,9,9a-Hexahydro-4a(4H)-dibenzofurancarboxaldehyde | --- | (183) |
| 3-Hydrazinodibenzofuran | 152 | (134) |
| | 174-5 | (6,133) |
| 2-(α-Hydroxy-β-aminoethyl)-dibenzofuran hydrochloride | 261 d. | (121) |
| 2-Hydroxydibenzofuran | --- | (141,148,184, 185,186) |
| | 134-5 | (111) |
| | 136 | (187) |
| | 132.5-3.5 | (188) |
| 3-Hydroxydibenzofuran | --- | (186) |
| | 139-9.5 | (135) |
| | 137-8 | (188) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 4-Hydroxydibenzofuran | 99-100 | (14,10,132, 189) |
| | 101-2 | (188) |
| | 102 | (190,191) |
| 2-(α-Hydroxy-β-diethylaminoethyl)-dibenzofuran hydrochloride | 157-9.5 | (121) |
| 2-(α-Hydroxy-β-dimethylaminoethyl)-dibenzofuran hydrochloride | 173-4 | (121) |
| 2-(α-Hydroxy-β-ethylaminoethyl)-dibenzofuran hydrochloride | 218-9.5 | (121) |
| 2-(α-Hydroxyethyl)-dibenzofuran | 67-7.5 | (8,110,122) |
| 2-(2-Hydroxy-2-naphthoylamino)-dibenzofuran | --- | (192) |
| 2-(α-Hydroxy-β-piperidinoethyl)-dibenzofuran hydrochloride | 245-251 | (121) |
| 4-Hydroxy-tetrahydrodibenzofuran | 111-3 | (141) |
| 4-Iododibenzofuran | 70-1 | (137) |
| | b.p.,180/ 3 mm. | |
| | 73-4 | (12) |
| | --- | (169,151) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Isobutyldibenzofuran | b.p.,195-6/ 16 mm. | (120) |
| 2-Isobutyryldibenzofuran | 57<br>b.p.,215-8/ 15 mm. | (120) |
| 4-(1-Isoquinolyl)-dibenzofuran | 137-8 | (119) |
| 2-Methoxydibenzofuran | 45.1<br>45-6<br>--- | (111)<br>(187)<br>(189,132,193) |
| 4-Methoxydibenzofuran | ---<br>54<br>b.p.,164-5/ 5 mm. | (189,119)<br>(132)<br>(190) |
| 3-[N-(p-Methoxyphenyl)-acetamido]-dibenzofuran | 154-5 | (98) |
| 3-[N-(p-Methoxyphenyl)-amino]-dibenzofuran | 173-4 | (12,98) |
| 3-Methylaminodibenzofuran hydrochloride | 245-7 d. | (110) |
| 2-Methyldibenzofuran | 44<br>b.p.,305/ 750 mm. | (140) |
| 3-Methyldibenzofuran | b.p.,303-4/ 756 mm. | (194) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 4-Methyldibenzofuran | 45 | (195,190) |
| α-Methyl-3-dibenzofuranmethanol | 63-4<br>b.p.,173-9/<br>2 mm. | (196) |
| 2-Methyldibenzofuran picrate | 99-100 | (140) |
| 3-Methyldibenzofuran picrate | 104 | (140) |
| Methyl 2-dibenzofurylcarbinol | --- | (105) |
| 3-Methyl-2-(2-dibenzofuryl)-cinchoninic acid | 298-300 d. | (120) |
| 3-Methyl-2-(2-dibenzofuryl)-quinoline | 110 | (120) |
| 3-Methyl-2-(2-dibenzofuryl)-quinoline picrate | 230 d. | (120) |
| x-Nitrodibenzofuran | 210<br>101-3<br>132-3 | (1)<br>(141)<br>(131) |
| 1-Nitrodibenzofuran | 120-1<br>126-6.5 | (160,109)<br>(103) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Nitrodibenzofuran | 147-9 | (3,131,160) |
| | 106-8 | (1) |
| | 158.5-9.5 | (103) |
| | 154-6 | (197) |
| | --- | (195,136,198) |
| 3-Nitrodibenzofuran | 181-2 | (110,8,3,131, 141,122) |
| | 186-6.5 | (103) |
| | 178-180 | (4,195,119, 156) |
| | 181-2 | (134) |
| 4-Nitrodibenzofuran | 138-9 | (103) |
| 7-Nitro-1,2,3,4-tetrahydro-dibenzofuran | 124 | (110,142) |
| Octadecylammonium 2-dibenzofuran-carboxylate | 88-9 | (155) |
| N-Octadecyl 2-dibenzofuran-carboxamide | 118-8.5 | (155) |
| o-Nitrophenyl-3-dibenzofurylamine | 139.5-140 | (9) |
| 3-Palmitoylaminodibenzofuran | 130 | (199) |
| Perhydrodibenzofuran | b.p.,108-110/ 7 mm. | (132) |
| 2-Phenylacetyldibenzofuran | 117 | (120) |

(Continued on next page)

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198 G. N. Lewis and M. Kasha, J. Am. Chem. Soc., 66, 2100 (1944).

199 G. M. Ford, Iowa State Coll. J. Sci., 12, 121 (1937).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| α-Phenyl-α-(1-dibenzofuryl)-acetone | 103-5 | (150) |
| α-Phenyl-α-(1-dibenzofuryl)-acetone oxime | 204-6 | (10,150) |
| 3-Phenyl-2-(2-dibenzofuryl)-cinchoninic acid | 247-251 d. | (120) |
| 3-Phenyl-2-(2-dibenzofuryl)-quinoline | 194 | (120) |
| 3-Phenyl-2-(2-dibenzofuryl)-quinoline picrate | 262-4 d. | (120) |
| 2-(Phenylsulfonyl)-dibenzofuran | 166 | (200) |
| 2- -piperidinoacetyldibenzofuran | --- | (110) |
| 3-Piperidinodibenzofuran hydrochloride | 258-260 | (110) |
| Piperidinemethyl-2-dibenzofuryl-carbinol hydrochloride | 242 | (110) |
| 2-Propionyldibenzofuran | 97 | (120) |
| | b.p.,229-231/ 16 mm. | |
| | 100-1 | (121) |
| 3-n-Propylaminodibenzofuran | b.p.,203-5/ 1 mm. | (110) |
| 3-Stearoylaminodibenzofuran | 134 | (199) |

(Continued on next page)

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200 German Patent 701,954 [C. A., 36, 99 (1942)].

201 S. Rajagopalan and K. Ganapathi, Proc. Indian Acad. Sci., 15A, 432 (1942) [C. A., 37, 1124 (1943)]

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 3-Sulfanilamidodibenzofuran | 245<br>246-7<br>242-3 | (8)<br>(123)<br>(201,124) |
| 3-Sulfanilamidodibenzofuran hydrochloride | --- | (8) |
| 4-Sulfanilamidodibenzofuran | 195 | (8) |
| 4-Sulfanilamidodibenzofuran hydrochloride | --- | (8) |
| 1,2,3,4-Tetrahydro-7-acetyldibenzofuran | ---<br>67 | (142)<br>(132) |
| 1,2,3,4-Tetrahydro-7-aminodibenzofuran hydrochloride | 269 | (110) |
| 1,2,3,4-Tetrahydro-7-aminodibenzofuran picrate | 187-8 | (202) |
| 3,4,4a,9b-Tetrahydrodibenzofuran-1-carboxylic acid | --- | (203) |
| 1,2,3,4-Tetrahydrodibenzofuran-7-carboxylic acid | 145-6 | (141) |
| 4-(m-Trifluoromethylbenzalamino)-dibenzofuran | 81-3 | (148,149) |
| 2-Valeryldibenzofuran | 99<br>b.p.,233-5/ 13 mm. | (120) |

(Continued on next page)

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203 A. R. Sengupta, N. C. Ganguly and D. K. Banerjee, Science and Culture, 12, 404 (1947).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Vinyldibenzofuran | --- | (204,180,205, 206,207,117) |
| | 30 b.p.,164/ 7 mm. | (115) |
| 3-Vinyldibenzofuran | 38-9 b.p.,127-8/ 1.5 mm. | (196) |
| DISUBSTITUTED DIBENZOFURANS | | |
| 3-Acetamino-4-acetoxyldibenzofuran | 209-210 | (7,160) |
| 2-Acetamino-3-bromodibenzofuran | 240-1 | (12) |
| 1-Acetamino-4-ethoxydibenzofuran | 218.5 | (170) |
| 3-Acetamino-6-iododibenzofuran | 268-9 | (7,129) |
| 1-Acetamino-2-methoxydibenzofuran | 203-5 | (111) |
| 1-Acetamino-4-methoxydibenzofuran | 222-3 | (119) |
| 2-Acetamino-3-nitrodibenzofuran | 206-8 | (131) |
| 2-Acetoxy-3-acetaminodibenzofuran | 209-210 | (111) |
| 2-Acetoxy-6-acetaminodibenzofuran | 198-9 | (111) |

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[204] U. S. Patent 2,500,733 [C. A., 44, 5390 (1950)].

[205] British Patent 604,879 [C. A., 43, 1220 (1949)].

[206] U. S. Patent 2,498,474 [C. A., 44, 6198 (1950)].

[207] British Patent 601,568 [C. A., 42, 7574 (1948)].

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Acetoxy-7-acetaminodibenzofuran | 200-2 | (111) |
| 2-Acetoxy-8-acetaminodibenzofuran | 187-8 | (111) |
| 2-Acetoxy-3-aminodibenzofuran | 235-8 | (111) |
| 2-Acetoxy-3-aminodibenzofuran oxazole | 136-7 | (111) |
| 2-Acetoxy-7-chlorodibenzofuran | 142-3 | (111) |
| 2-Acetoxy-6-chlorodibenzofuran | 118-9 | (111) |
| 2-Acetoxy-1-dibenzofurancarboxylic acid | 151-2 | (8,122) |
| 2-Acetoxy-7-methyldibenzofuran | 131-2 | (111) |
| 2-Acetoxy-8-methyldibenzofuran | 117-8 | (111) |
| 2-Acetoxy-3-nitrodibenzofuran | 157-9 | (111) |
| 2-Acetyl-7-acetaminodibenzofuran oxime | 203 | (105,144) |
| 2-Acetyl-7-aminodibenzofuran | 158-9 | (144) |
| 2-Acetyl-6-carbomethoxydibenzofuran | 174-5 | (208) |
| 2-Acetyl-6-dibenzofurancarboxylic acid | 262-5 | (208) |
| 3-Acetyl-2-hydroxydibenzofuran | 168-9<br>b.p.,227/<br>7 mm. | (7) |

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[208] J. C. Bailie, Doctoral Dissertation, Iowa State College, 1938.

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1-Acetyl-4-methoxydibenzofuran | 134-4.5 | (119) |
| 1-Acetyl-4-methoxydibenzofuran oxime | 176-7.5 | (119) |
| 3-Acetyl-4-methoxydibenzofuran oxime | 162.5-165 | (112) |
| 2-Acetyl-7-nitrodibenzofuran | 212-3 | (105,144) |
| 1-Amino-4-acetaminodibenzofuran | 202 | (109,160) |
| 3-Amino-4-acetaminodibenzofuran | 236-7 | (7) |
| 1-Amino-2-acetoxydibenzofuran | 208-9 | (111) |
| 1-Amino-2-acetoxydibenzofuran oxazole | 144-5 | (111) |
| 2-Amino-3-benzenesulfoxamidodibenzofuran | 227-8 | (108) |
| 2-Aminobenzofuro-[2,3f]-benzothiazole | 268-9 | (105,144) |
| 2-Aminobenzofuro-[2,3f]-benzothiazole hydrochloride | 300 d. | (105,144) |
| 2-Amino-3-bromodibenzofuran | 172-3 | (131) |
| 3-Amino-2-dibenzofurylthiocyanate | 175 | (119) |
| 1-Amino-4-[(8-diethylsulfamyl-3-dibenzofuryl)-amino]-anthraquinone-2-sulfonic acid | --- | (126) |
| 1-(α-aminoethyl)-4-methoxydibenzofuran hydrochloride | 268-9 | (209) |

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209 T. H. Cook and H. Gilman, Proc. Iowa Acad. Sci., 46, 220 (1939).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 4-Amino-6-hydroxydibenzofuran | 191.5-2.5 | (133) |
| 1-Amino-2-hydroxydibenzofuran hydrochloride | --- | (4) |
| 3-Amino-4-hydroxydibenzofuran hydrochloride | 275 | (7,160) |
| 3-Amino-6-iododibenzofuran | 143-4 | (12,129) |
| 1-Amino-2-methoxydibenzofuran | 96-7<br>92.5 | (111)<br>(98) |
| 1-Amino-3-methoxydibenzofuran | 92.5 | (12) |
| 1-Amino-4-methoxydibenzofuran | 103-4 | (12,98) |
| 2-Amino-7-methoxydibenzofuran | 169-170 | (111) |
| 4-Amino-6-methoxydibenzofuran | 109 | (133) |
| 1-Amino-4-methoxydibenzofuran hydrochloride | --- | (105) |
| 2-Amino-4-methoxydibenzofuran hydrochloride | --- | (105) |
| 3-Amino-4-methoxydibenzofuran | --- | (105) |
| 4-Amino-6-methoxydibenzofuran | 235-6 | (133) |
| 1-Amino-4-(1-methoxy-2-dibenzofurylamino)-anthraquinone-2-sulfonic acid | --- | (126) |
| 2-Amino-7-methyldibenzofuran | 128-9 | (111) |
| 2-Amino-3-nitrodibenzofuran | 207-9 | (131) |
| 7-Amino-7,8,9,10-tetrahydrobenzo-[b]-naphtho-[2,3d]-furan hydrochloride | 266-7 | (105) |

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1-Benzeneazo-4-hydroxydibenzofuran | 174-5 | (210) |
| 2-Benzeneazo-3-hydroxydibenzofuran. | 166<br>177-8 | (125)<br>(211) |
| Benzofuro-[2,3f]-quinoline | 106-6.5 | (108) |
| Benzofuro-[3,2g]-quinoline | 168-9 | (108) |
| Benzofuro-[2,3f]-quinoline hydrochloride | 240-265 | (121,212) |
| Benzofuro-[3,2g]-quinoline hydrochloride | 216-233 | (121,212) |
| 2-Benzoyl-x-carbomethoxy-dibenzofuran | 189-190 | (122) |
| 2-Benzoyl-x-dibenzofurancarboxylic acid | 265-6 | (122) |
| 2,7-Bis-(5-benzamido-1-anthraquinonylamino)-dibenzofuran | --- | (213) |
| 2,7-Bis-(4-benzoylamino-1-anthraquinonylamino)-dibenzofuran | --- | (214) |

(Continued on next page)

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210 H. Gilman and M. W. Van Ess, J. Am. Chem. Soc., 61, 3146 (1939).

211 M. W. Van Ess, Iowa State Coll. J. Sci., 12, 167 (1937).

212 E. Mosettig and R. A. Robinson, J. Am. Chem. Soc., 57, 902 (1935).

213 Swiss Patent 216,594 [C. A., 42, 5232 (1948)].

214 Swiss Patent 216,595 [C. A., 42, 5232 (1948)].

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2,8-Bis-(chloroacetyl)-dibenzofuran | 202 | (215) |
| 3,2-Bis-(diethylaminoethylamino)-dibenzofuran | b.p.,250-260/ 1 mm. | (171) |
| 3,7-Bis-[(diethylaminoethyl)-guanylguanido]-dibenzofuran | 132 | (172) |
| 2,7-Bis-(γ-diethylaminopropylamino)-dibenzofuran | b.p.,285-290/ 0.1 mm. | (12,98) |
| 2,8-Bis-(γ-diethylaminopropylamino)-dibenzofuran | b.p.,240-5/ 0.1 mm. | (12,98) |
| 3,7-Bis-(guanylguanido)-dibenzofuran | 216 | (172) |
| 2,8-Bis-[1-hydroxy-2-(1-piperidyl)ethyl]-dibenzofuran | 181 | (215) |
| 2,8-Bis-(1-piperidylacetyl)-dibenzofuran | 161 | (215) |
| 1-Bromo-4-acetaminodibenzofuran | 228 | (125) |
| 2-Bromo-3-acetaminodibenzofuran | 194 | (134) |
| 2-Bromo-8-acetyldibenzofuran | 192 | (120) |
| 1-Bromo-2-acetoxydibenzofuran | 135-6 | (148) |
| 1-Bromo-2-aminodibenzofuran | 120-1 | (150) |
| 2-Bromo-7-aminodibenzofuran | --- | (37) |

(Continued on next page)

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215 M. Tomita, J. Pharm. Soc. Japan, 56, 906 (1936) [C. A., 31, 3484 (1937)]

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Bromo-3-aminodibenzofuran hydrochloride | 236 d. | (110) |
| 2-Bromo-7-aminodibenzofuran hydrochloride | --- | (131,110) |
| x-Bromo-4-carbomethoxydibenzofuran | 240 | (3) |
| 2-Bromo-4-dibenzofuran-carboxylic acid | 284-5 | (8,153) |
| 2-Bromo-8-dibenzofuran-carboxylic acid | 328 | (119,141) |
| 2-(8-Bromo-2-dibenzofuryl)-cinchoninic acid | 290-5 d. | (120) |
| 2-(8-Bromo-2-dibenzofuryl)-quinoline | 172 | (120) |
| 2-(8-Bromo-2-dibenzofuryl)-quinoline | 172 | (120) |
| 2-(8-Bromo-2-dibenzofuryl)-quinoline picrate | 235-240 | (120) |
| 1-Bromo-4-γ-diethylamino-propylaminodibenzofuran | b.p.,212-5/ 0.1 mm. | (12) |
| 2-Bromo-3-γ-diethylamino-propylaminodibenzofuran | b.p.,190-5/ 0.5 mm. | (12,98) |
| 1-(2-Bromoethyl)-4-methoxy-dibenzofuran | 91-91.5 | (119) |
| x-Bromo-1-hydroxydibenzofuran | 178 | (156) |
| 1-Bromo-2-hydroxydibenzofuran | 122-3 | (148) |

(Continued on next page)

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1-Bromo-3-hydroxydibenzofuran | 113-3.5 | (216) |
| 1-Bromo-4-hydroxydibenzofuran | 150 | (125) |
| 2-Bromo-3-hydroxydibenzofuran | 111-2<br>115-6 | (5)<br>(125,188) |
| 2-Bromo-4-hydroxydibenzofuran | 154-5 | (12) |
| 4-Bromo-6-hydroxydibenzofuran | 138-9 | (133) |
| 1-Bromo-2-methoxydibenzofuran | --- | (125,217) |
| 1-Bromo-4-methoxydibenzofuran | 97-97.5 | (105,144,125, 217) |
| 2-Bromo-4-methoxydibenzofuran | 106-7 | (12) |
| 4-Bromo-6-methoxydibenzofuran | 114 | (133,217) |
| 2-Bromo-4-methyldibenzofuran | 106-6.5 | (211) |
| 2-Bromo-3-nitrodibenzofuran | 154.5-5.5 | (131,4) |
| 2-Bromo-7-nitrodibenzofuran | 250.5-1.5<br>248<br>258-9 | (131)<br>(110)<br>(103) |
| 2-Bromo-8-phenylacetyldibenzofuran | --- | (120) |
| 7-Bromopyridodibenzofuran | 152 | (110) |
| 1-Carbomethoxy-4-methoxy-dibenzofuran | 125 | (217) |

(Continued on next page)

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216 K. Tatematsu and B. Kubota, Bull. Chem. Soc. Japan, 9, 448 (1934) [C. A., 29, 1091 (1935)].

217 H. Gilman, J. Swislowsky and G. E. Brown, J. Am. Chem. Soc., 62, 348 (1940).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1-Chloroacetyl-4-methoxy-dibenzofuran | 165-6 | (133) |
| 2-Chloro-7-aminodibenzofuran | --- | (37) |
| x-Chloro-2-dibenzofuran-carboxylic acid | 285-290 | (141) |
| 1-Chloro-4-hydroxydibenzofuran | 154-5 | (14) |
| 1-Chloro-8-hydroxydibenzofuran | 148-9 | (111) |
| 3-[4-(2-Chloromethyl-3-chloro-benzofuro-[3,2g]-quinolyl)-amino]-dibenzofuran | 240-2 | (127) |
| 1,4-Diacetaminodibenzofuran | 307-8 | (109,160) |
| 3,4-Diacetaminodibenzofuran | 257 | (7) |
| 3,6-Diacetaminodibenzofuran | 321-2 | (12,129) |
| 3,7-Diacetaminodibenzofuran | 322-4 | (218) |
| 4,6-Diacetaminodibenzofuran | 297-8 | (133) |
| 4,8-Diacetaminodibenzofuran | 265-6 | (219) |
| 1,8-Diacetoxydibenzofuran | 128-130 | (111) |
| 2,7-Diacetoxydibenzofuran | 164-5 | (111) |
| 2,8-Diacetoxydibenzofuran | 154-5 | (111) |

(Continued on next page)

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218 S. Yamashiro, J. Chem. Soc. Japan, 59, 945 (1938) [C. A., 33, 603 (1939)].

219 S. Yamashiro, ibid., 59, 186 (1938) [C. A., 32, 9084 (1938)].

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 3,4-Diacetoxydibenzofuran | 104-5 | (133) |
| 4,6-Diacetoxydibenzofuran | 177 | (133) |
| 2,8-Diacetyldibenzofuran | 140<br>b.p.,250-260/<br>15 mm. | (118) |
| 2,8-Diallyloxydibenzofuran | 70-1 | (9) |
| 1,4-Diaminodibenzofuran | 86-7 | (7,109,160) |
| 2,3-Diaminodibenzofuran | --- | (128) |
| 2,7-Diaminodibenzofuran | 125 | (1) |
| 3,6-Diaminodibenzofuran | 154-5 | 12,129) |
| 3,7-Diaminodibenzofuran | 150.5-2.5 | (218) |
| 4,6-Diaminodibenzofuran | 152 | (133) |
| 1,4-Diaminodibenzofuran dihydrochloride | 322-3 | (109,160) |
| 2,3-Diaminodibenzofuran dihydrochloride | --- | (131,110) |
| 2,7-Diaminodibenzofuran dihydrochloride | --- | (1,131) |
| 4,6-Diaminodibenzofuran dihydrochloride | 298 | (133) |
| 4,6-Diaminodibenzofuran picrate | 213 d. | (133) |
| 2,8-Dibenzofurandiacetic acid | 230-1 | (118) |

(Continued on next page)

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| Dibenzofurandicarboxamide | 307-8 | (220) |
| 2,8-Dibenzofurandicarboxylic acid | ---<br>300 | (141,142,119)<br>(215) |
| 4,6-Dibenzofurandicarboxylic acid | 325 | (190,221,157) |
| 4,6-Dibenzofurandisulfinic acid | 183-5 | (190) |
| 2,8-Dibenzofurandisulfonic acid | --- | (142,163) |
| 4,6-Dibenzofurandisulfonic acid | 300 | (190) |
| 2,8-Dibenzofurandisulfonylchloride | 218 | (141) |
| Dibenzofuran-2-sulfonic acid-8-sulfonyl chloride | 128-130 | (141) |
| 4-(Dibenzofurotetrahydroquinolyl)-aminodibenzofuran | 300 | (127) |
| 2,8-Dibenzofuryloxyacetic acid | 271-3 d. | (9) |
| 2,3-Dibromodibenzofuran | 153-4 | (110) |
| 2,7-Dibromodibenzofuran | ---<br>178-9 | (131)<br>(135) |
| 2,8-Dibromodibenzofuran | 187-189<br>b.p.,220/8 mm.<br>--- | (7)<br><br>(14,120,119,142,156) |
| Dibromotetrahydrodibenzofuran | 79 | (132) |

(Continued on next page)

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[220] French Patent 803,257 [C. A., 31, 2615 (1937)].

[221] H. Gilman and R. V. Young, J. Am. Chem. Soc., 57, 1121 (1935).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2,8-Dibutyryldibenzofuran | 136<br>b.p.,280-5/<br>17 mm. | (120) |
| 2,8-Dicarbomethoxydibenzofuran | 166-7 | (141,215) |
| x,x-Dichlorodibenzofuran | 144 | (1) |
| 2,8-Dichlorodibenzofuran | 184-5 | (14) |
| 2,8-Dicyanodibenzofuran | --- | (141,142) |
| 1-β-Diethylaminoethyl-4-methoxydibenzofuran hydrochloride | 187 d. | (119) |
| 2-γ-Diethylaminopropylamino-3-bromodibenzofuran | b.p.,200-210/<br>0.5 mm. | (12,98) |
| 3-γ-Diethylaminopropylamino-6-iododibenzofuran | b.p.,290-5/<br>0.5 mm. | (12,98) |
| 1-γ-Diethylaminopropylamino-2-methoxydibenzofuran | b.p.,205-7/<br>0.1 mm. | (12,98) |
| 1-γ-Diethylaminopropylamino-4-methoxydibenzofuran | b.p.,211-5/<br>0.1 mm. | (12,98) |
| 3-γ-Diethylaminopropylamino-4-methoxydibenzofuran | b.p.,231-4/<br>0.3 mm. | (12,98) |
| 4,4a-Dihydro-4-(p-methoxyphenyl)-2(3)-dibenzofuranone | 152 | (222) |
| 4a,10b-Dihydro-4a,8-dimethyl-2(1)-dibenzofuranone | --- | (223) |

(Continued on next page)

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223 W. W. Westerfeld and C. Lowe, J. Biol. Chem., 145, 463 (1942).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1,8-Dihydroxydibenzofuran | 184-5 | (111) |
| 1,9-Dihydroxydibenzofuran | 215 | (224) |
| 2,7-Dihydroxydibenzofuran | 196-7 | (111) |
| 2,8-Dihydroxydibenzofuran | 241-2<br>239-240<br>230-235<br>--- | (9)<br>(111)<br>(225)<br>(8,10,122) |
| 3,4-Dihydroxydibenzofuran | 161-4 | (7) |
| 3,7-Dihydroxydibenzofuran | 241-1.5 | (224) |
| 4,6-Dihydroxydibenzofuran | 203-4<br>190 | (12,129,133)<br>(190) |
| 4,6-Diiododibenzofuran | 160 | (12,129,190) |
| 1,8-Dimethoxydibenzofuran | 70-1 | (111) |
| 2,7-Dimethoxydibenzofuran | 112-3<br>b.p.,197-8/<br>3 mm. | (111) |
| 2,8-Dimethoxydibenzofuran | 89-90<br>88-9 | (111)<br>(225) |
| 3,4-Dimethoxydibenzofuran | 60-1 | (133) |
| 4,6-Dimethoxydibenzofuran | 128-9 | (133,12) |
| 4,6-Dimethoxydibenzofuran picrate | 161-2 | (133) |

(Continued on next page)

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224 T. Simsda and K. Hata, Sci. Papers Inst. Phys. Chem. Research (Tokyo), 35, 365 (1939) [ C. A., 33, 4594 (1939) ].

225 H. Gilman, J. Swiss, H. B. Willis and F. A. Yeoman, J. Am. Chem. Soc., 66, 798 (1944).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1-(Dimethylaminomethyl)-2-hydroxydibenzofuran | 114-5 | (185) |
| 4a,7-Dimethyl-1,2,3,4,4a,9b-hexahydrodibenzofuran | b.p.,139-141/12 mm. | (226) |
| x,x'-Dinitrodibenzofuran | 195-200 | (1) |
| 2,6-Dinitrodibenzofuran | 263-4 | (103,219) |
| 2,7-Dinitrodibenzofuran | ---<br>255-6 | (1)<br>(103,219) |
| 2,8-Dinitrodibenzofuran | 329-330 | (103,135,219) |
| 3,7-Dinitrodibenzofuran | 326-7 | (103,218) |
| 4,6-Dinitrodibenzofuran | 351-2 | (103) |
| 2,8-Dipropionyldibenzofuran | 141 | (120) |
| γ,γ'-Dioxodibenzofuran-2,8-dicrotonic acid | 222 | (227) |
| 1-Ethoxalyl-4-methoxydibenzofuran | 113 | (133) |
| N-(6-Ethoxy-2-benzothiazolyl)-2-hydroxy-3-dibenzofuran carboxamide | --- | (228) |

(Continued on next page)

226 J. B. Niederl and V. Niederl, ibid., 61, 1785 (1939).

227 B. J. Cramer, W. Schroeder, W. J. Moran, C. H. Nield, M. Edwards, C. I. Jarowski and B. Puetzer, J. Am. Pharm. Assoc., 37, 439 (1948).

228 U. S. Patent 2,399,026 [C. A., 40, 3909 (1946)].

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Ethoxy-3-(3-hydroxy-2-naphthoyl-amino)-dibenzofuran | 236-7 | (229) |
| 2-Hydroxy-6-acetaminodibenzofuran | 210-1 | (111) |
| 2-Hydroxy-7-acetaminodibenzofuran | 244-5 | (111,230) |
| 2-Hydroxy-8-acetaminodibenzofuran | 210-3 | (111) |
| 2-Hydroxy-3-aminodibenzofuran | 205 | (187) |
| 2-Hydroxy-6-aminodibenzofuran | 230-2 | (111) |
| 2-Hydroxy-7-aminodibenzofuran | 200-2 | (111,230) |
| 2-Hydroxy-8-aminodibenzofuran | 269-270 | (111) |
| 2-Hydroxy-3-aminodibenzofuran hydrobromide | 265 d. | (187) |
| 1-Hydroxy-(2 or 4)-bromo-dibenzofuran | 178 | (5) |
| 2-Hydroxy-3-bromodibenzofuran | 143-4 | (125,139) |
| 2-Hydroxy-6-chlorodibenzofuran | 167-9 | (111) |
| 2-Hydroxy-7-chlorodibenzofuran | 167-8 | (111) |
| 2-Hydroxy-8-chlorodibenzofuran | 184-5<br>--- | (111)<br>(186) |
| 2-Hydroxy-1-dibenzofuran-carboxylic acid | 216 d. | (8,122) |

(Continued on next page)

[229] French Patent 818,074 [C. A., 32, 2366 (1938)].

[230] British Patent 470,021 [C. A., 32, 1487 (1938)].

Table IV (Continued)

| Name of Compound | M.P.° | Reference |
|---|---|---|
| 2-Hydroxy-3-dibenzofuran-carboxylic acid | 292-3<br>--- | (187)<br>(228,231) |
| 2-Hydroxy-9-dibenzofuran-carboxylic acid | 246-7 | (111) |
| 2-Hydroxy-2',5'-dimethoxy-3-dibenzofurancarboxanilide | --- | (187,232,233, 234) |
| 1-β-Hydroxyethyl-4-methoxy-dibenzofuran | 96-6.5 | (119) |
| 2-Hydroxy-7-methoxydibenzofuran | 146-7<br>b.p.,230/ 3 mm. | (111) |
| 2-Hydroxy-8-methoxydibenzofuran | 116-8 | (111) |
| 4-Hydroxy-6-methoxydibenzofuran | 109-110 | (133) |
| 2-Hydroxy-6-methyldibenzofuran | 131-3<br>b.p.,170/ 3 mm. | (111) |
| 2-Hydroxy-7-methyldibenzofuran | 148-9<br>--- | (111)<br>(186) |
| 2-Hydroxy-8-methyldibenzofuran | 160-1 | (111) |

(Continued on next page)

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[231] U. S. Patent 2,453,105 [C. A., 43, 3040 (1949)].

[232] U. S. Patent 2,496,255 [C. A., 44, 7545 (1950)].

[233] U. S. Patent 2,500,080 [C. A., 44, 8122 (1950)].

[234] A. Semard, Teintex, 4, 76 (1939) [C. A., 33, 5386 (1939)].

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Hydroxy-4'-(4-morpholinyl)-3-dibenzofurancarboxanilide | --- | (235,236) |
| 2-Hydroxy-4'-(4-morpholinyl)-3'-nitro-3-dibenzofurancarboxanilide | --- | (235,237) |
| 2-Hydroxy-3-nitrodibenzofuran | 209-210 | (111) |
| 7-Keto-8-dimethylaminomethyl-7,8,9,10-tetrahydrobenzo-[b]-naphtho-[2,3d]-furan hydrochloride | 185-6 | (119) |
| 2-Methoxy-3-acetaminodibenzofuran | 139-140 | (111) |
| 2-Methoxy-7-acetaminodibenzofuran | 177-8 | (111) |
| 2-Methoxy-8-acetaminodibenzofuran | 178-9 | (111) |
| 2-Methoxy-3-aminodibenzofuran | 92-2.5<br>92<br>93-4<br>--- | (12)<br>(111)<br>(187)<br>(126) |
| 2-Methoxy-6-aminodibenzofuran | 81-2 | (111) |
| 2-Methoxy-7-aminodibenzofuran | 92-3 | (111) |
| 2-Methoxy-8-aminodibenzofuran | 120-1 | (111) |
| 5-Methoxy-1-benz-[b]-indeno-[4,5d]-3(2)-one | 192-3 | (10,150) |

(Continued on next page)

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235 British Patent 613,130 [C. A., 43, 8162 (1949)].

236 U. S. Patent 2,419,932 [C. A., 42, 607 (1948)].

237 U. S. Patent 2,408,421 [C. A., 41, 1451 (1947)].

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Methoxy-3-bromodibenzofuran | 171-2 | (12,148,125, 217,139) |
| | 170.5-1.5 | (187) |
| 2-Methoxy-8-bromodibenzofuran | 92.5 | (139) |
| 2-Methoxy-3-carbomethoxy-dibenzofuran | 122.5 | (156) |
| 4-Methoxy-6-carbomethoxy-dibenzofuran | --- | (189) |
| 2-Methoxy-6-chlorodibenzofuran | 106-8 | (111) |
| 2-Methoxy-7-chlorodibenzofuran | 83-4 | (111) |
| 2-Methoxy-8-chlorodibenzofuran | 86-8 | (111) |
| 2-Methoxy-3-cyanodibenzofuran | 197-9 | (187) |
| 4-Methoxy-1-dibenzofuranacetamide | 203 | (238) |
| 4-Methoxy-1-dibenzofuran-acrylic acid | 281-282 | (150) |
| 4-Methoxy-1-dibenzofuran-carboxaldehyde | 104-5 | (150) |
| 2-Methoxy-1-dibenzofuran-carboxylic acid | 156-7 | (217) |
| 2-Methoxy-3-dibenzofuran-carboxylic acid | 206-7 | (7,217) |
| | 208-9 | (187) |
| 4-Methoxy-1-dibenzofuran-carboxylic acid | 279-280 | (119,10,238) |
| | 280-1 | (217) |
| | 276-77 | (133) |

(Continued on next page)

[238] A. Burger and S. Avakian, J. Am. Chem. Soc., 62, 226 (1940).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 4-Methoxy-3-dibenzofuran-carboxylic acid | 182-3 | (189) |
| 4-Methoxy-6-dibenzofuran-carboxylic acid | 240-2 | (189,217) |
| 4-Methoxy-1-dibenzofuran-carboxylic acid chloride | 162.5-3.5 | (238) |
| 4-Methoxy-1-dibenzofuryl-acetic acid | 220 | (150) |
| 4-Methoxy-1-dibenzofuryl-α-oxoacetic acid | 187 | (133) |
| 4-Methoxy-1-dibenzofuryl-α-oxoacetic acid semicarbazone | 211.5-212 | (133) |
| β-[1-(4-Methoxydibenzofuryl)]-propionic acid | 176-7 | (150) |
| 2-Methoxy-2-γ-diethylamino-propylaminodibenzofuran | b.p.,210-3/ 0.1 mm. | (12,98) |
| 1-Methoxy-8-hydroxydibenzofuran | 145-6 | (111) |
| 2-Methoxy-3-(3-hydroxy-2-naphthoylamino)-dibenzofuran | ---<br>227-9 | (187)<br>(229) |
| 2-Methoxy-1-methyldibenzofuran | 60-1 | (150) |
| 2-Methoxy-6-methyldibenzofuran | 77-9 | (111) |
| 2-Methoxy-7-methyldibenzofuran | 50-1 | (111) |
| 2-Methoxy-3-nitrodibenzofuran | 186-6.5<br>190-2 | (12,98)<br>(111) |
| 1-Methyl-2-acetoxydibenzofuran | 80-1 | (150) |
| 2-Methyl-1-benzofuro-[2,3f]-benzimidazole | 270 | (144) |

(Continued on next page)

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Methyl-1-benzofuro-[2,3f]-benzimidazole hydrochloride | 335 | (144,105) |
| 6-Methyl-4-dibenzofurancarboxylic acid | 238-240 | (190) |
| 4a-Methyl-7-ethyl-1,2,3,4,4a,9b-hexahydrodibenzofuran | b.p.,146-8/12 mm. | (226) |
| 1-Methyl-2-hydroxydibenzofuran | 135-6 | (150) |
| 1-Methyl-8-hydroxydibenzofuran | 137-8 | (111) |
| N-Methyl-1,2,3,4-tetrahydrobenzofuro-[3,2g]-quinoline | 56-7 | (121) |
| N-Methyl-1,2,3,4-tetrahydrobenzofuro-[2,3f]-quinoline | 72-3 | (121) |
| N-Methyl-1,2,3,4-tetrahydrobenzofuro-[3,2g]-quinoline hydrochloride | 198-205 d. | (121,212) |
| N-Methyl-1,2,3,4-tetrahydrobenzofuro-[2,3f]-quinoline hydrochloride | 196-215 | (121,212) |
| 1-Nitro-4-acetaminodibenzofuran | 216 | (160) |
| 2-Nitro-3-acetaminodibenzofuran | 196<br>205 | (105,8)<br>(108) |
| 2-Nitro-7-acetaminodibenzofuran | 212 | (1) |
| 1-Nitro-2-acetoxydibenzofuran | 134-5 | (111) |
| 1-Nitro-4-aminodibenzofuran | 219-220 | (160,109) |
| 2-Nitro-3-aminodibenzofuran | 222<br>232-3 | (128)<br>(108) |

(Continued on next page)

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Nitro-3-benzenesulfonamido-dibenzofuran | 226-7 | (108) |
| 2-Nitro-3-bis-(phenylsulfonyl)-aminodibenzofuran | 263-5 d. | (108) |
| 3-Nitro-6-bromodibenzofuran | 205 | (119) |
| 1-Nitro-8-bromodibenzofuran | 189.5-190.5 | (103) |
| 2-Nitro-6-carbomethoxydibenzofuran | 205.5 | (4) |
| 3(or 7)-nitro-4-carbomethoxy-dibenzofuran | 156-8 | (3) |
| 3-Nitro-6-carbomethoxydibenzofuran | 156-8 | (3) |
| 3-Nitro-7-carbomethoxydibenzofuran | 202-3 | (119) |
| x-Nitro-4-dibenzofuran-carboxylic acid | 132-146 | (3) |
| 7-Nitro-2-dibenzofuran-carboxylic acid | 300 d. | (152) |
| 3(or 7)-Nitro-4-dibenzofuran-carboxylic acid | 160-5 d. | (3) |
| x-Nitro-x-dibenzofuran-sulfonic acid | --- | (141) |
| 3-Nitro-x-dibenzofuran-sulfonic acid | --- | (1) |
| 3-Nitro-x-dibenzofuran-sulfonyl chloride | 200 | (1) |
| 2-Nitro-7-dibenzofurylarsine oxide | 250 | (136) |
| 2-Nitro-7-dibenzofuryl-dichloroarsine | 152 | (136) |

(Continued on next page)

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1-Nitro-2-hydroxydibenzofuran | 130-2 | (111) |
| 2-Nitro-3-hydroxydibenzofuran | 162-3 | (12,98) |
| 3-Nitro-6-iododibenzofuran | 223 | (119) |
| 2-Nitro-3-iododibenzofuran | 189-9.5 | (12,98) |
| 1-Nitro-2-methoxydibenzofuran | 154-5 | (111) |
| 1-Nitro-4-methoxydibenzofuran | 153.5-4 | (12) |
| 2-Nitro-3-[N-(p-methoxyphenyl)amino]-dibenzofuran | 173-4 | (98) |
| 3-Phenyl-2-(8-bromo-2-dibenzofuryl)-cinchoninic acid | 280 d. | (120) |
| 3-Phenyl-2-(8-bromo-2-dibenzofuryl)-quinoline | 196 | (120) |
| 3-Phenyl-2-(8-bromo-2-dibenzofuryl)-quinoline picrate | 235 | (120) |
| Pyrido-[2,3c]-dibenzofuran hydrochloride | 292-4 | (110) |
| 2-Sulfo-7-dibenzofuranarsine oxide | 275 | (136) |
| 2-Sulfo-7-dibenzofuranarsonic acid | 300 | (136) |
| 1,2,3,4-Tetrahydrobenzofuro-[2,3f]-quinoline | 80-1 | (121) |
| 1,2,3,4-Tetrahydrobenzofuro-[3,2g]-quinoline | 111-2 | (121) |
| 1,2,3,4-Tetrahydrobenzofuro-[2,3f]-quinoline hydrochloride | 230-245 | (121,212) |

(Continued on next page)

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1,2,3,4-Tetrahydrobenzofuro-[3,2g]-quinoline hydrochloride | 196-226 | (121,212) |
| 3,4,4a,9b-Tetrahydro-6(?)-hydroxy-1(2H)-dibenzofuranone | 134-5 | (239) |
| 3,4,4a,9b-Tetrahydro-9b-hydroxy-2(1H)-dibenzofuranone | b.p.,157-160/3 mm. | (175) |
| 1,2,3,4-Tetrahydropyrido-[2,3c]-dibenzofuran hydrochloride | 225-235 | (240) |
| 1-(m-Trifluoromethylphenylazo)-2-hydroxydibenzofuran | 173-4 | (148,149) |
| TRISUBSTITUTED DIBENZOFURANS | | |
| 1-Acetamino-3,4-dimethoxy-dibenzofuran | 196-6.5 | (133) |
| 1-Acetamino-4,6-dimethoxy-dibenzofuran | 244-5 | (133) |
| 2-Acetyl-7-acetamino-8-nitro-dibenzofuran | 270-1 | (144) |
| 1-Acetyl-3,4-dimethoxydibenzofuran | 90.5-91 | (133) |
| 1-Acetyl-4,6-dimethoxydibenzofuran | 178-9 | (133) |
| 1-Acetyl-3,4-dimethoxydibenzofuran oxime | 156-7 | (133) |

(Continued on next page)

[239] E. C. Horning, M. G. Horning and E. J. Platt, ibid., 70, 2072 (1948).

[240] E. Mosettig and R. A. Robinson, ibid., 58, 688 (1936).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1-Acetyl-4,6-dimethoxydibenzofuran oxime | 203-4 | (133) |
| 5-Aminobenzofuro-[2,3f]-quinoline | 197-8 | (108) |
| 5-Aminobenzofuro-[3,2f]-quinoline | 138-140 | (108) |
| Aminobenzofuro-[2,3f]-quinoline | 233 | (108) |
| Aminobenzofuro-[2,3f]-quinoline | 200 | (108) |
| Aminobenzofuro-[3,2g]-quinoline | 236.5-237 | (108) |
| 1-Amino-3,4-dimethoxydibenzofuran | 162-3 | (133,12,98) |
| 1-Amino-4,6-dimethoxydibenzofuran | 162-2.5 | (133) |
| 1-Amino-4,6-dimethoxydibenzofuran hydrochloride | 286-7 | (133) |
| 1-Amino-2-methoxy-4-(4'-nitrophenylazo)-dibenzofuran | 267 | (111) |
| 1-Benzeneazo-4,6-dimethoxydibenzofuran | 170 | (133) |
| 1-Benzeneazo-4-hydroxy-6-methoxydibenzofuran | 175 | (133) |
| 5-Benzenesulfonamidobenzofuro-[3,2f]-quinoline | 197-8 | (108) |
| 4-[p-(Benzyloxy)phenyl]-2,3,4,4a-tetrahydro-2-oxo-3-carboethoxydibenzofuran | 156 | (241) |

(Continued on next page)

[241] S. N. Rao and R. S. Wheeler, J. Chem. Soc., 1004 (1939).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 4-[p-(Benzyloxy)phenyl]-2,3,4,4a-tetrahydro-2-oxo(?)-3-dibenzofurancarboxylic acid | 202 | (241) |
| 2-Bromo-3-acetamino-6-carbomethoxydibenzofuran | 247-7.5 | (211) |
| 1-Bromo-3-acetamino-4-methoxydibenzofuran | 178-9 | (119) |
| 1-Bromo-3-amino-4-methoxydibenzofuran | 135-6 | (119) |
| Bromobenzofuro-[2,3f]-quinoline | 204 | (108) |
| Bromobenzofuro-[2,3f]-quinoline | 180-2 | (108) |
| 1-Bromo-3-γ-diethylaminopropylamino-4-methoxydibenzofuran | b.p.,245-250/ 0.1 mm. | (12,98) |
| 1(?)-Bromo-2,8-diacetoxydibenzofuran | 142-4<br>143-5 | (148)<br>(10) |
| 1(?)-Bromo-2,8-dihydroxydibenzofuran | --- | (148,10) |
| 1(?)-Bromo-2,8-dimethoxydibenzofuran | 102.5-3.5 | (148) |
| 1-Bromo-3,4-dimethoxydibenzofuran | 108 | (133,217) |
| 1-Bromo-4,6-dimethoxydibenzofuran | 152 | (133,150,217) |
| 3-Bromo-2,8-dimethoxydibenzofuran | 115-6<br>117.5-118 | (10,150)<br>(9) |
| 3-Bromo-4,6-dimethoxydibenzofuran | 117.5-119 | (10,150) |

(Continued on next page)

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Bromo-3,7-dinitrodibenzofuran | 254-5 | (242) |
| 2-Bromo-3,8-dinitrodibenzofuran | 216-7 | (242) |
| 3-Bromo-2,7-dinitrodibenzofuran | 223-4 | (242) |
| 3-Bromo-2,8-dinitrodibenzofuran | 254-5 | (242) |
| 8-Bromo-1,7-dinitrodibenzofuran | 198-9 | (242) |
| 1-Bromo-3-hydroxy-4-methoxydibenzofuran | 161-2 | (133) |
| 1-Bromo-3-nitro-4-methoxydibenzofuran | 160-1 | (119) |
| 1-(5-Chloro-2,4-dimethoxyphenylazo)-2-hydroxy-2',5'-dimethoxy-3-dibenzofurancarboxanilide | --- | (232) |
| 2,8-Diacetamino-3-nitrodibenzofuran | 322-4 | (122) |
| 4,6-Diamino-1-dibenzofurancarboxylic acid | 183-4 | (150) |
| 1,3-Diamino-2-methoxydibenzofuran | 117-8 | (111) |
| 2,8-Diamino-3-nitrodibenzofuran | 210-3 | (150) |
| Diazomethyl 4,6-dimethoxy-1-dibenzofuryl ketone | 151 d. | (133) |
| 1,x-Dibromo-2-acetoxydibenzofuran | 154-5 | (148) |
| 1,3-Dibromo-2-acetaminodibenzofuran | 254-8 | (9) |
| 2,8-Dibromo-3-acetyldibenzofuran | 157-7.5 | (119) |

(Continued on next page)

[242] S. Yamashiro, Bull. Chem. Soc. Japan, 17, 76 (1942).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1,3-Dibromo-2-aminodibenzofuran | 181.5-182<br>180-1 | (9)<br>(10,150) |
| 1,x-Dibromo-2-hydroxydibenzofuran | 168-178 | (148) |
| 1,3-Dibromo-2-hydroxydibenzofuran | 112-3 | (9) |
| 1,2-Dibromo-4-methoxydibenzofuran | 127-8 | (12) |
| 1,3-Dibromo-4-methoxydibenzofuran | 139-140 | (150) |
| 2,7-Dibromo-3-nitrodibenzofuran | 209-210 | (242) |
| 2,8-Dibromo-1-nitrodibenzofuran | 245-7 | (242) |
| 2,8-Dibromo-3-nitrodibenzofuran | 190-1 | (242) |
| 3,8-Dibromo-2-nitrodibenzofuran | 205-6 | (242) |
| 1,2-Dicarbomethoxy-4-methoxy-dibenzofuran | 165-6<br>175-6 | (12)<br>(10,150) |
| 1,3-Dichloro-4-hydroxydibenzofuran | 160-1 | (14) |
| 5-[4-Diethylamino-1-methylbutyl-amino]-benzofuro-[3,2f]-quinoline | b.p., 230-250/ 0.01 mm. | (108) |
| (3-Diethylaminopropylamino)-benzo-furo-[3,2g]-quinoline | b.p., 250-260/ 0.02 mm. | (108) |
| 1-γ-Diethylaminopropylamino-3,4-dimethoxydibenzofuran | b.p.,240-3/ 0.1 mm. | (12,98) |
| 1-[5-(Diethylsulfamyl)-2-methoxy-phenylazo]-2-hydroxy-4'-(4-morpholinyl)-3'-nitro 3-dibenzofurancarboxanilide | --- | (237) |
| x,x-Dihydro,x,x-dibromo-3-amino-dibenzofuran | 186 d. | (174) |

(Continued on next page)

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1-(2,3-Dihydro-6-methoxy-3-benzofuryl)-2-hydroxy-7-methoxy(?)-dibenzofuran | 184-5 | (243) |
| 3,4-Dihydro-7-methoxy-1-(6-methoxy-3(2H)-benzofurylidene)-2(1H)-dibenzofuranone | 184-5 | (243) |
| 4,4a-Dihydro-7-methoxy-4-(p-methoxyphenyl)-2(3)-dibenzofuranone | 154 | (222) |
| 4,6-Dihydroxy-1-dibenzofurancarboxylic acid | 278-280 | (150) |
| 3,4-Dimethoxy-1-carbomethoxydibenzofuran | 78 | (217) |
| 4,6-Dimethoxy-1-carbomethoxydibenzofuran | 163 | (133) |
| 2,8-Dimethoxy-3-dibenzofurancarboxaldehyde | 166-7 | (10,150) |
| 4,6-Dimethoxydibenzofuran-1-aldehyde | 162-4 | (150) |
| 2,8-Dimethoxy-1-dibenzofurancarboxylic acid | --- | (150) |
| 2,8-Dimethoxy-3-dibenzofurancarboxylic acid | 170-1 | (10,150) |
| 3,4-Dimethoxy-1-dibenzofurancarboxylic acid | 236 | (217) |
| 4,6-Dimethoxy-1-dibenzofurancarboxylic acid | 297-8 | (150,217) |

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[243] J. A. Barltrop, J. Chem. Soc., 958 (1946).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 4,6-Dimethoxy-1-dibenzofuran-carboxylic acid chloride | 147-150 | (133) |
| γ-(4,6-Dimethoxy-1-dibenzofuroyl)-butyric acid | 197-8 | (12) |
| β-(4,6-Dimethoxy-1-dibenzofuroyl)-propionic acid | 241-2 | (12) |
| 4,6-Dimethoxy-1-dibenzofuryl-acetamide | 210-1 | (133) |
| 4,6-Dimethoxy-1-dibenzofuryl-acetic acid | 205.5-6.5 | (133) |
| 2,7-Dimethoxy-3-(3-hydroxy-2-naphthoylamino)-dibenzofuran | 232-3 | (229) |
| 2,8-Dimethoxy-1-methyldibenzofuran | 85-6 | (150) |
| 4,6-Dimethoxy-γ-oxo-1-dibenzo-furanbutyric acid | --- | (150) |
| 4,6-Dimethoxy-γ-oxo-3(?)-dibenzo-furanbutyric acid | 167-8 | (10,150) |
| 1,3-Dimethyl-8-hydroxydibenzofuran | 162-4 | (111) |
| 2,3-Dimethyl-8-hydroxydibenzofuran | 194-5 | (111) |
| 1,x-Dinitro-4-acetaminodibenzofuran | 288 | (160) |
| 3,x-Dinitro-4-acetaminodibenzofuran | 277-8 | (109) |
| x,x-Dinitro-4-carbomethoxy-dibenzofuran | 230-1 | (3) |
| 2,7-Dinitro-x-dibenzofuran-sulfonic acid | --- | (141) |
| 1,3-Dinitro-2-hydroxydibenzofuran | 240 d. | (111) |

(Continued on next page)

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 3,8-Dinitro-4-hydroxydibenzofuran | 225 d. | (7) |
| 1,3-Dinitro-2-methoxydibenzofuran | 188-9 | (111) |
| 1-Ethyl-2,8-dihydroxydibenzofuran | 142-3 | (150) |
| 1-Ethyl-2,8-dimethoxydibenzofuran | 71-2 | (150) |
| Ethyl-2,3,4,4a-tetrahydro-4-(2-methoxy-1-naphthyl)-2-oxo-3-dibenzofurancarboxylate | 174 | (244) |
| Ethyl-2,3,4,4a-tetrahydro-4-(2-methoxy-1-naphthyl)-2-oxo-3-dibenzofurancarboxylate oxime | 188 | (244) |
| 2-Hydroxy-7,8-dichlorodibenzofuran | 203-4 | (111) |
| 3-Hydroxy-4,6-dimethoxydibenzofuran | 140-1 | (10,150) |
| 2-Hydroxy-6,7-dimethyldibenzofuran | 127-9 | (111) |
| 4-Hydroxy-3-nitro-1-dibenzofurancarboxylic acid | 269-270 | (12) |
| γ-(4-Methoxy-2-bromo-1-dibenzofuroyl)-propionic acid | 194-5 | (12) |
| 4-Methoxy-1,2-cyclopentenodibenzofuran | 66-8 | (10,150) |
| 2-Methoxy-3-(3-hydroxy-2-naphthoylamino)-7-chlorodibenzofuran | 268-270 | (229) |
| 2-Methoxy-3-(3-hydroxy-2-naphthoylamino)-7-methyldibenzofuran | 254-6 | (229) |

(Continued on next page)

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Methoxy-3-(3-hydroxy-2-naphthoylamino)-8-methyldibenzofuran | 230-1 | (229) |
| γ-(4-Methoxy-3-nitro-1-dibenzofuroyl)-butyric acid | 169-170 | (12) |
| 2-Methyl-8-acetyl-1-benzofuro-[2,3f]-benzimidazole | 298 | (105,144) |
| 2-Methyl-8-acetyl-1-benzofuro-[2,3f]-benzimidazole hydrochloride | 325 d. | (105,144) |
| 1-Methyl-2,8-dihydroxydibenzofuran | 187-8 | (150) |
| 1-Methyl-2-hydroxy-8-aminodibenzofuran hydrochloride | 220 d. | (150) |
| 2-Methyl-5-methoxydibenzofuro-[1,2d]-imidazole hydrochloride | 306-7 d. | (105) |
| [3-(4-Morpholinyl)-propylamino]-benzofuro-[3,2g]-quinoline | 120 | (108) |
| 5-Nitrobenzofuro-[2,3f]-quinoline | 206-7 | (108) |
| Nitrobenzofuro-[2,3f]-quinoline | 282 | (108) |
| Nitrobenzofuro-[2,3f]-quinoline | 297-8 | (108) |
| Nitrobenzofuro-[3,2g]-quinoline | 267-8 | (108) |
| 1-Nitro-2,8-dimethoxydibenzofuran | 158-9 | (9) |
| 1-Nitro-3,4-dimethoxydibenzofuran | 146-7 | (12,98) |
| 3-Nitro-2,8-dimethoxydibenzofuran | 172-4 | (9) |
| 2,3,4,4a-Tetrahydro-4-(p-methoxyphenyl)-2-oxo-3-carboethoxydibenzofuran | 159 | (222) |

(Continued on next page)

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2,3,8-Triaminodibenzofuran | --- | (8,122) |
| Tribromotetrahydrodibenzofuran | 148 | (132) |
| 1-(m-Trifluoromethylphenylazo)-2,8-dihydroxydibenzofuran | 256-7 | (148,149) |
| 3,4,6-Trimethoxydibenzofuran | 126-7 | (10,150) |
| 3,4,7-Trimethoxydibenzofuran | ---<br>75-6 | (245)<br>(246) |
| Trinitrodibenzofuran | 223 | (1) |
| 2,3,7-Trinitrodibenzofuran | 276.5-7.5 | (103,218) |
| 2,3,8-Trinitrodibenzofuran | 237-8 | (103,247) |
| 2,4,6-Trinitrodibenzofuran | 260-1 | (103) |
| 2,4,8-Trinitrodibenzofuran | 312-3 | (103,247) |
| TETRASUBSTITUTED DIBENZOFURANS | | |
| 9-Bromo-4,6-dimethoxy-γ-oxo-3-dibenzofuranbutyric acid | 200-1 | (150) |
| 2-Bromo-3,6,8-Trinitrodibenzofuran | 251-2 | (242) |
| 2-Bromo-3,7,8-Trinitrodibenzofuran | 254-5 | (242) |

(Continued on next page)

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[247] S. Yamashiro, J. Chem. Soc. Japan, 59, 443 (1938).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 3-Bromo-2,7,8-Trinitrodibenzofuran | 248-9 | (242) |
| 1,9(?)-Diacetamino-2,8-dimethoxy-dibenzofuran | 175-7 | (148) |
| 1,9(?)-Diamino-2,8-dimethoxy-dibenzofuran | --- | (9,148) |
| 2,7-Diamino-3,8-dinitrodibenzofuran | 360.5-1.5 | (219) |
| Dibenzofurantetrasulfonic acid | --- | (141,142) |
| Dibenzofurantetrasulfonylchloride | 250 d. | (141) |
| 2,8-Dibromo-4,6-diacetamino-dibenzofuran | 358-260 | (135) |
| 1,9(?)-Dibromo-2,8-diacetoxy-dibenzofuran | 173-4 | (9,148) |
| 1,9(?)-Dibromo-2,8-dihydroxy-dibenzofuran | ---<br>181-5 | (9)<br>(148) |
| 1,9-Dibromo-4,6-dihydroxy-dibenzofuran | 239-240 | (133) |
| 1,3-Dibromo-4,6-dimethoxy-dibenzofuran | 173.5-174 | (133) |
| 1,9(?)-Dibromo-2,8-dimethoxy-dibenzofuran | ---<br>195-6<br>196-7 | (9)<br>(148)<br>(10,150, 217,225) |
| 1,9(?)-Dibromo-4,6-dimethoxy-dibenzofuran | 173-4<br>167-8 | (10,150)<br>(133) |
| 2,7-Dibromo-3,8-dinitrodibenzofuran | 262-3 | (242) |
| 2,8-Dibromo-1,7-dinitrodibenzofuran | 273-4 | (242) |

(Continued on next page)

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2,8-Dibromo-3,7-dinitrodibenzofuran | 297-8 | (242) |
| 1,3-Dibromo-4-hydroxy-6-methoxy-dibenzofuran | 177-8 | (133) |
| 1,9(?)-Dicarbomethoxy-2,8-dimethoxy-dibenzofuran | 128-9 | (148,217) |
| 2,8-Dihydroxy-1,9(?)-bisphenylazo-dibenzofuran | 165-6<br>155-6 | (8)<br>(122) |
| 2,8-Dihydroxy-3,7-dibromodibenzo-furan | 260-1 | |
| 2,8-Dihydroxy-1,9(?)-dibenzofuran-dicarboxylic acid | 313-4 | (148) |
| 2,8-Dihydroxy-3,7-dimethyl-dibenzofuran | 232<br>231-2 | (8,122)<br>(225) |
| 2,8-Dimethoxy-1,9(?)-dibenzofuran-dicarboxaldehyde dioxime | 243-4 | (148) |
| 2,8-Dimethoxy-1,9(?)-dibenzofuran dicarboxylic acid | 270-1<br>270-2 | (8,122,217)<br>(148) |
| 2,8-Dimethoxy-3,7-dibenzofuran-dicarboxylic acid | 290 d. | (217) |
| 2,8-Dimethoxy-3,7-dibromo-dibenzofuran | 260-1 | (10) |
| 2,8-Dimethoxy-3,7-dicarbome-thoxydibenzofuran | 183-4 | (217) |
| 2,8-Dimethoxy-3,7-dimethyl-dibenzofuran | 144-4.5 | (225) |
| 1,7-Dimethyl-2,8-dimethoxy-dibenzofuran | 104-6 | (10) |

(Continued on next page)

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1,9(or 1,7-)-Dimethyl-2,8-dimethoxydibenzofuran | 129-131 | (10) |
| 7-Ethyl-2,8-dimethoxy-1-methyldibenzofuran picrate | 144-4.5 | (150) |
| 1-Methyl-7-bromo-2,8-dimethoxydibenzofuran | 144-5<br>143-5 | (9)<br>(10,150) |
| 2,3,4,4a-Tetrahydro-7-methoxy-4-(p-methoxyphenyl)-2-oxo-3-carboethoxydibenzofuran | 146 | (222) |
| 2,3,7,8-Tetrahydroxydibenzofuran | 285 d. | (248) |
| 2,4,6,8-Tetrahydroxydibenzofuran | 300 d. | (249) |
| Tetranitrodibenzofuran | 284 | (1) |
| 2,3,6,8-Tetranitrodibenzofuran | 249-250 | (103,247) |
| 2,3,7,8-Tetranitrodibenzofuran | 285-6<br>286-7 | (103)<br>(247,218) |
| 2,4,6,8-Tetranitrodibenzofuran | 249-250<br>262-3 | (250)<br>(103,247) |
| 3,4,7-Trimethoxydibenzofuran-1-propionic acid | 146-8 | (245) |

(Continued on next page)

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Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| PENTASUBSTITUTED DIBENZOFURANS | | |
| 2-Bromo-1,3,6,8-tetranitro-dibenzofuran | 285-6 | (242) |
| 2-Bromo-1,3,7,8-tetranitro-dibenzofuran | 278-9 | (242) |
| 2-Bromo-1,3,7,9-tetranitro-dibenzofuran | 329 d. | (242) |
| 1,9(?)-Dibromo-2,8-dihydroxy-3(?)-nitrodibenzofuran | 267-8 | (9) |
| 1,9(?)-Dibromo-2,8-dimethoxy-3(?)-nitrodibenzofuran | 243-4 | (9) |
| Dibromo-1-methyl-2,8-dihydroxy-dibenzofuran | 191-2 | (10) |
| 2,7-Dibromo-1,3,8-trinitro-dibenzofuran | 257-8 | (242) |
| 2,8-Dibromo-1,3,7-trinitro-dibenzofuran | 275-6 | (242) |
| 2,8-Dibromo-3,4,6-trinitro-dibenzofuran | 334-4.5 | (242) |
| 4,6-Dibromo-2,3,8-trinitro-dibenzofuran | 297-8 | (242) |
| 3,9b-Dihydro-7-methoxy-1,9b-dimethyl-3-oxo-2-carbomethoxy-dibenzofuran | 101 | (251) |

(Continued on next page)

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[251] R. T. Foster, A. Robertson and R. V. Healy, J. Chem. Soc., 1594 (1939).

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 3,9b-Dihydro-7-methoxy-1,9b-dimethyl-3-oxo-2-dibenzofurancarboxylic acid | --- | (252) |
| 3,9b-Dihydro-7-methoxy-1,9b-dimethyl-3-oxo-2-dibenzofurancarboxylic acid hydrate | 147 | (251) |
| 2,3,4,4a-Tetrahydro-2-oxo-4(p-methoxyphenyl)-7-(benzyloxy)-8-bromo-3-carboethoxydibenzofuran | 205-6 | (253) |
| 1,3,9-Tribenzeneazo-4,6-dimethoxydibenzofuran | 191-3 | (133) |
| 2,3,8-Tribromo-1,7-dinitrodibenzofuran | 256-7 | (242) |
| 1,4,8-Tri-p-nitrobenzoyloxy-3,7-dimethoxydibenzofuran | 300 | (254) |
| HEXASUBSTITUTED DIBENZOFURANS | | |
| 1,9(?)-Diamino-2,8-dimethoxy-3,7-diacetaminodibenzofuran | 295-6 d. | (9) |
| 1,9(?)-Dibromo-2,8-dihydroxy-3,7(?)-dinitrodibenzofuran | 204 | (9) |
| 1,9(?)-Dibromo-2,8-dimethoxy,3,7(?)-dinitrodibenzofuran | 222-3 | (9) |

(Continued on next page)

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253 R. P. Dodwadmath, J. Univ. Bombay, 9, 172 (1940) [C. A., 35, 6959 (1941)].

254 H. G. H. Erdtman, Proc. Roy. Soc. (London), A143, 177 (1934) [C. A., 28, 1338 (1934)].

Table IV (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2,8-Dibromo-1,3,7,9-tetranitrodibenzofuran | 352-4 d. | (242) |
| 3,9b-Dihydro-7-methoxy-1,6,9b-trimethyl-3-oxo-2-carboethoxydibenzofuran | 115 | (251) |
| 3,9b-Dihydro-7-methoxy-1,6,9b-trimethyl-3-oxo-2-dibenzofurancarboxylic acid | ---<br>150 | (252)<br>(251) |
| 2,8-Dihydroxy-3,7(?)-dibromo-1,9(?)-dibenzofurandicarboxylic acid | 318-9 | (148) |
| 2,8-Dihydroxy-3,7(?)-dibromo-1,9(?)-dicarbomethoxydibenzofuran | 268-9 | (9) |
| 2,8-Dimethoxy-3,7(?)-dibromodibenzofuran-1,9(?)-dicarboxylic acid | --- | (9) |
| 2,8-Dimethoxy-3,7(?)-dibromo-1,9(?)-dicarbomethoxydibenzofuran | 230-1 | (9) |
| 2,8-Dimethoxy-1,3,7,9(?)-tetraaminodibenzofuran | 181-2 | (9) |
| 2,8-Dimethoxy-1,3,7,9(?)-tetranitrodibenzofuran | 246-7 | (9) |
| 1,2,3,5a,9a,9b-Hexahydro-1,7,9,9b-tetramethyl-3-oxo-2-dibenzofurancarboxylic acid | --- | (252) |
| 2,3,6,8-Tetrabromo-1,7-dinitrodibenzofuran | 329-330 | (242) |
| 2,3,6,8-Tetrabromo-4,7-dinitrodibenzofuran | 297-8 | (242) |
| 2,3,7,8-Tetrabromo-1,9-dinitrodibenzofuran | 364-5 d. | (242) |

(Continued on next page)

Table IV (Concluded)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1,3,7,9(?)-Tetranitro-2,8-dihydroxydibenzofuran | 246-7 | (148) |
| 1,3,7,9(?)-Tetranitro-2,8-dimethoxydibenzofuran | 245-6 | (148) |
| HEPTASUBSTITUTED DIBENZOFURANS | | |
| 1,9(?)-Dibromo-2,8-dimethoxy-2,4,7(?)-trinitrodibenzofuran | 212.5-214 | (9) |
| OCTASUBSTITUTED DIBENZOFURANS | | |
| 2,8-Dimethoxy-3,4,6,7(?)-tetranitrodibenzofuran-1,9(?)-dicarboxylic acid | 247-9 | (9) |
| 2,8-Dimethoxy-3,4,6,7(?)-tetranitro-1,9(?)-dicarbomethoxydibenzofuran | 199.5-200 | (9) |

Table V

Additional Derivatives of Dibenzofuran

| Name of Compound | M.P. | Reference |
|---|---|---|
| MONOSUBSTITUTED DIBENZOFURANS | | |
| 2-Acetyldibenzofuran | b.p.,218-220/ 18 mm. | (255) |
| 2-Amyldibenzofuran | b.p.,210-2/ 13 mm. | (255) |
| β-Bromo-γ-oxo-3-dibenzofuran-butyric acid | --- | (256) |
| 2-Dibenzofuransulfonic acid | --- | (257) |
| 2-(2-Dibenzofuryl)-indole | 200 b.p.,330/ 17 mm. | (255) |
| 2-Ethyldibenzofuran | b.p.,180-2/ 13 mm. | (255) |
| 2-Heptanoyldibenzofuran | 75 b.p.,250-3/ 13 mm. | (255) |
| 2-Heptyldibenzofuran | b.p.,222-5/ 17 mm. | (255) |

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Table V (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Octanoyldibenzofuran | 82-3<br>b.p.,285-7/<br>30 mm. | (255) |
| 2-Octyldibenzofuran | b.p.,235/<br>15 mm. | (255) |
| γ-Oxo-3-dibenzofuranbutyric acid | --- | (256) |
| γ-Oxo-3-dibenzofurancrotonic acid | --- | (256) |
| 2-(β-1-piperidylpropionyl)-<br>dibenzofuran hydrochloride | 226.5-8.3 d. | (258) |
| 2-Propyldibenzofuran | b.p.,198-9/<br>14 mm.<br>b.p.,190-2/<br>12 mm. | (255) |
| 2-(2-Thienyl)-dibenzofuran | 120<br>b.p., 280/<br>18 mm. | (255) |
| 2-Vinyldibenzofuran | --- | (259) |
| DISUBSTITUTED DIBENZOFURANS | | |
| 2-Acetyl-8-amyldibenzofuran | b.p., 250/<br>12 mm. | (255) |
| 2-Acetyl-8-ethyldibenzofuran | 88 | (255) |

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Table V (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Acetyl-8-heptyldibenzofuran | b.p., 268/ 15 mm. | (255) |
| 2-Acetyl-8-octyldibenzofuran | b.p.,288-292/ 20 mm. | (255) |
| 2-Acetyl-8-propyldibenzofuran | b.p.,236-8/ 13 mm. | (255) |
| 3,7-Diaminodibenzofuran | --- | (260,261) |
| 2,8-Dicyanodibenzofuran | 299 | (262) |
| 3,7-Dihydroxydibenzofuran | --- | (263,264) |
| 2-(8-Ethyl-2-dibenzofuryl)-cinchoninic acid | 140 | (255) |
| 2-(8-Ethyl-2-dibenzofuryl)-quinoline | 113 | (255) |
| 2-(8-Ethyl-2-dibenzofuryl)-quinoline picrate | 210 | (255) |
| 2-Ethyl-8-propionyldibenzofuran | b.p.,240-5/ 13 mm. | (255) |

(Continued on next page)

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262 J. S. Moffatt, J. Chem. Soc., 625 (1951).

263 Y. Asahina and M. Aoki, J. Pharm. Soc. Japan, 64, 41 (1944) [C. A., 45, 2928 (1951)].

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Table V (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 3,6-Guanyldibenzofuran dihydrochloride | 320 | (262) |
| 2-(8-Heptyl-2-dibenzofuryl)-cinchoninic acid | 115 | (255) |
| 3-Methyl-2-(8-ethyl-2-dibenzofuryl)-cinchoninic acid | 175 | (255) |
| 3-Methyl-2-(8-ethyl-2-dibenzofuryl)-quinoline | --- | (255) |
| 3-Methyl-2-(8-ethyl-2-dibenzofuryl)-quinoline picrate | --- | (255) |
| 3-Methyl-2-(8-propyl-2-dibenzofuryl)-cinchoninic acid | 164 | (255) |
| 2-(8-Octyl-2-dibenzofuryl)-cinchoninic acid | 110 | (255) |
| 2-Propionyl-8-propyldibenzofuran | b.p.,250/19 mm. | (255) |
| 2-(8-Propyl-2-dibenzofuryl)-cinchoninic acid | 145 | (255) |
| 2-(8-Propyl-2-dibenzofuryl)-quinoline | 116 | (255) |
| 2-(8-Propyl-2-dibenzofuryl)-quinoline picrate | 196-200 d. | (255) |
| TRISUBSTITUTED DIBENZOFURANS | | |
| 4a,9b-Dihydro-4a,8-dimethyl-2(1H)-dibenzofuranone | 128 | (265) |

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Table V (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 4a,9b-Dihydro-4a,8-dimethyl-2(1H)-dibenzofuranone oxime | 195 | (265) |
| 1-Methyl-3,7-dihydroxydibenzofuran | ---<br>212 | (264)<br>(266) |
| TETRASUBSTITUTED DIBENZOFURANS | | |
| 1-Amyl-3,7-diacetoxy-9-propyl-dibenzofuran | --- | (264) |
| 1-Amyl-3,7-dihydroxy-9-propyl-dibenzofuran | ---<br>120 | (267,264)<br>(268) |
| 1-Amyl-3,7-dimethoxy-9-propyl-dibenzofuran | 31 | (267,268) |
| 1-Amyl-3-hydroxy-7-methoxy-9-propyldibenzofuran | 81-2 | (268) |
| 3,7-Dimethoxy-1,9-dibenzofuran-dicarboxylic acid | 323<br>321-3 d. | (267)<br>(268) |
| 3,7-Dimethoxy-1,9-dicarbomethoxy-dibenzofuran | 189<br>188.5-9.5 | (267)<br>(268) |
| 3,7-Dimethoxy-1,9-dimethyl-dibenzofuran | ---<br>157 | (264,266)<br>(268) |

(Continued on next page)

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Table V (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 1,9-Dimethyl-3,7-dihydroxydibenzofuran | --- | (263,268, 264,266) |
| 1-Methyl-3,7-dihydroxy-8-dibenzofurancarboxylic acid | 308 | (266) |
| 1-Methyl-3,7-dimethoxy-9-dibenzofurancarboxylic acid | ---<br>181 | (266)<br>(268) |
| PENTASUBSTITUTED DIBENZOFURANS | | |
| 1-Amyl-3-hydroxy-7-methoxy-9-propyl-2-dibenzofurancarboxylic acid | 173 | (267,268, 264,269) |
| 1-(Hydroxymethyl)-3,7-dihydroxy-9-methyl-2-dibenzofurancarboxylic acid 1,2-lactone | 324 | (266) |
| 1-Propyl-3,7-dimethoxy-8-carbomethoxy-9-dibenzofurancarboxylic acid | --- | (268) |
| 1-Propyl-3,7-dimethoxy-8,9-dibenzofurandicarboxylic acid | 209-210 d. | (268) |
| 1-Propyl-3,7-dimethoxy-8,9-dicarbomethoxydibenzofuran | 130-1 | (268) |
| HEXASUBSTITUTED DIBENZOFURANS | | |
| 1,4,6,9-Tetramethyl-3,7-dihydroxydibenzofuran | --- | (263,264) |

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Table VI

Derivatives of Dibenzothiophene

| Name of Compound | M.P. | Reference |
|---|---|---|
| MONOSUBSTITUTED DIBENZOTHIOPHENES | | |
| 2-Decyldibenzothiophene | b.p.,289-290/ 16 mm. | (255) |
| 1-(2-Dibenzothienyl)-3-phenyl-2-propen-1-one | 154-5 | (270) |
| 1-(p-Dimethylaminophenyl)-3-(2-dibenzothienyl)-2-propen-1-one | 163-4 | (270) |
| 2-Heptyldibenzothiophene | b.p.,258/ 18 mm. | (255) |
| 3-Methyldibenzothiophene | --- | (271) |
| 2-Octyldibenzothiophene | b.p.,280-5/ 20 mm. | (255) |
| 1-Phenyl-3-(2-dibenzothienyl)-2-propen-1-one | 154-5 | (270) |
| 2-[β-Phenyl-β-(4-methoxy-3-acetaminophenyl)sulfonyl-propionyl]-dibenzothiophene | 175-7 | (270) |
| 2-(β-Phenyl-β-p-tolylsulfonyl-propionyl)-dibenzothiophene | 180-2 | (270) |
| 2-Tetradecyldibenzothiophene | 52-3<br>b.p.,305-310/ 12 mm. | (255) |

(Continued on next page)

[270] H. Gilman and L. F. Cason, J. Am. Chem. Soc., 72, 3469 (1950).

[271] D. F. DeTar and S. V. Sagmanli, ibid., 72, 965 (1950).

Table VI (Continued)

| Name of Compound | M.P. | Reference |
|---|---|---|
| DISUBSTITUTED DIBENZOTHIOPHENES | | |
| 2-Acetamino-8-ethoxydibenzothiophene | 195.5-6.5 | (272) |
| Alkyldibenzothiophenesulfonic acids | --- | (273) |
| 2-Amino-8-ethoxydibenzothiophene | 109-110 | (272) |
| Di-tert-amyldibenzothiophene | b.p.,200-220 | (274) |
| 2-Ethoxy-8-nitrodibenzothiophene | 209.5-210.5 | (272) |
| TRISUBSTITUTED DIBENZOTHIOPHENES | | |
| 2-Acetamino-4-iodo-8-ethoxydibenzothiophene | 214.5-215 | (272) |
| x-Amino-di-tert-amyldibenzothiophene | --- | (274) |
| 2-Amino-4-iodo-8-ethoxydibenzothiophene | 148.5-9.5 | (272) |
| x-Nitro-di-tert-amyldibenzothiophene | --- | (274) |
| 2-Nitro-4-iodo-8-ethoxydibenzothiophene | 222 | (272) |
| DIBENZOTHIOPHENE-5-DIOXIDES | | |
| 2-Acetamino-8-ethoxydibenzothiophene-5-dioxide | 313 | (272) |

(Continued on next page)

272 P. Block, Jr., ibid., 72, 5641 (1950).

273 U. S. Patent 2,527,334 [C. A., 45, 344 (1951)].

274 U. S. Patent 2,528,785 [C. A., 45, 1762 (1951)].

Table VI (Concluded)

| Name of Compound | M.P. | Reference |
|---|---|---|
| 2-Acetamino-4-iodo-8-ethoxydibenzo-thiophene-5-dioxide | 289 | (272) |
| 2-Amino-8-(2-pyridylamino)-dibenzo-thiophene-5-dioxide | --- | (275) |
| 2,8-Diaminodibenzothiophene-5-dioxide | 329-331 | (275) |
| 2,8-Dibromodibenzothiophene-5-dioxide | 341.0-3.5 | (275) |
| 2-Nitro-4-iodo-8-ethoxydibenzo-thiophene-5-dioxide | 300 | (272) |
| Sodium 2,8-diaminodibenzothiophene-5-dioxide bis-(formaldehyde-sulfoxylate) | 276.5-8.5 | (275) |

[275] U. S. Patent 2,529,860 [C. A., 45, 2984 (1951)].

# EXPERIMENTAL

## Dibenzofuran Derivatives

### Preparation of 3-nitrodibenzofuran

Early studies of the nitration of dibenzofuran have been recorded by Kirkpatrick.[110] Since nitration of dibenzofuran, contrary to other similar substitution reactions, involves the 3-position, this reaction has received much attention in the past in establishing the product, and in attempts to vary conditions in order to obtain the 2-nitro derivative. The only study since the review mentioned above is that of Yamashiro.[197,103] Employing methods similar to those of Kirkpatrick and of Borsche and Bothe,[134] Yamashiro reports not only the 3-nitro derivative (71%) but also the 2-nitro (10%) and the 1-nitro (1%) compounds. However, this work is open to some question for two reasons: first, attempts to repeat some procedures of Yamashiro in these Laboratories have not been successful; and, second, Yamashiro reports two widely varying melting points for his 1-nitro compound, 91-93°[197] and 126-126.5°.[103]

Several runs were made, varying the conditions, and the following procedure was found to be the most satisfactory. A suspension of 168 g. (1 mole) of dibenzofuran in 700 ml.

of glacial acetic acid was placed in a two-liter, three-necked flask, fitted with a dropping funnel, thermometer and Tru-bore stirrer. With rapid stirring, 152 ml. (3.6 moles) of fuming nitric acid (sp. gr. 1.50) was added at a moderate rate. The reaction is exothermic and if the rate of addition became too rapid, it was necessary to cool the flask with an ice bath; the internal temperature was not allowed to go above 65°. By the time the addition of the nitric acid was complete, all of the dibenzofuran had dissolved. Stirring was continued and about 5 minutes later a heavy precipitate formed. The mass was broken up and filtered. A purer product was obtained if the solid was not washed with water, but merely dried for some time on a Buchner funnel and then air dried. The yield of crude product, melting over the range 170-180°, was 200 g. (94%). One recrystallization from glacial acetic acid (again without washing with water) brought the melting point to 181-182°.

Preparation of 3-aminodibenzofuran

Many reductions of 3-nitrodibenzofuran were run and a modification of the catalytic reduction of Bradley[132] was found the most successful. The active Raney nickel catalyst was prepared by the method of Covert and Adkins.[276] For

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[276] L. W. Covert and H. Adkins, J. Am. Chem. Soc., 54, 4116 (1932).

good yields relatively pure 3-nitrodibenzofuran free from solvents such as acetic acid should be used. The Parr low pressure hydrogenation apparatus was employed and best yields were obtained with not more than 25 g. of the 3-nitro compound (bottle capacity 250 ml.). When the hydrogenation bottle is steam heated the reaction proceeds at a more rapid rate; however such heating was found unnecessary. Best yields were obtained with recently prepared catalyst. Platinum oxide may also be employed as a catalyst; however, if several reductions are to be run, Raney nickel is preferred because of its lower cost and the elimination of a troublesome recovery.

Twenty-five grams of 3-nitrodibenzofuran were suspended in 175 ml. of absolute ethanol in the hydrogenation bottle and an ethanolic suspension of Raney nickel containing about 1 g. of the catalyst was added. The hydrogenation was started at a pressure of 50 lbs./in.$^2$ and maintained above 25 lbs./in.$^2$ by refilling. Shaking was continued until the hydrogen pressure became constant (about 40 lbs./in.$^2$ absorbed). The solution was filtered free from the catalyst and the filtrate diluted with considerable water. The amine precipitated, sometimes first as an oil which soon solidified, and was filtered. One recrystallization from petroleum ether (b.p., 77-115°) gave 18.4 g. (85.5%) of dendritic, colorless crystals, melting at 99-100°. If older and less

active catalyst was employed, a lower melting product was obtained and was more difficult to purify.

Bromination of 2-bromo-3-acetaminodibenzofuran

2-Bromo-3-acetaminodibenzofuran was prepared from the 3-amino compound by a procedure based on that of Kirkpatrick.[104] A partial solution of 5 g. (0.016 mole) of 2-bromo-3-acetaminodibenzofuran in 75 ml. of glacial acetic acid was placed in a 250-ml. three-necked flask fitted with a dropping funnel, stirrer, condenser, and hydrogen bromide trap. This mixture was exposed to ultraviolet radiation and 2.7 g. (0.017 mole) of bromine was slowly added. The mixture was stirred for 2 hours at room temperature and finally for 2 hours at reflux temperature. Hydrogen bromide was evolved. Filtration of the cooled reaction mixture gave a grey solid melting over the range 170-195°. Recrystallization from absolute ethanol yielded 3.9 g. (62%) of product, melting from 220-230°. Two recrystallizations from glacial acetic acid brought the melting point to 233-236°; the yield was 2 g. (32%). A mixed melting point with the product obtained by bromination of 2-bromo-7-acetaminodibenzofuran was considerably depressed.

Anal. Calcd. for $C_{14}H_9O_2NBr_2$: Br, 41.80. Found: Br, 42.22, 42.15.

In one run a small amount of a product melting from 271-274° was obtained. In another run employing carbon

tetrachloride as a solvent only starting material was recovered.

Preparation of 2-bromodibenzofuran

The following is a modification of the procedure of Gilman and Avakian[98] and that of Buu-Hoi and Royer.[120] Into a three-necked, one-liter flask, fitted with a stirrer, dropping funnel, and hydrogen bromide trap was placed a solution of 84 g. (0.5 mole) of dibenzofuran in 500 ml. of glacial acetic acid. The solution was exposed to radiation from a mercury-vapor lamp and 80 g. (0.5 mole) of bromine very slowly added. After the bromine addition was complete (2 hours), stirring was continued at room temperature for 2 hours. The solution was then diluted with water and the resulting solid filtered. The crude product was dried and subsequently vacuum distilled. The principal fraction distilled from 150-160° at a pressure of 1 mm. The resulting white solid weighed 81.3 g. (65.5%) and melted from 97-105°. Two recrystallizations from petroleum ether (b.p. 60-70°) gave 64 g. (53%) melting at 108-109°. A bromination procedure using N-bromosuccinimide has been reported,[120] but the use of this reagent under similar conditions gave a very crude product with considerable recovery of starting material.

Reductive debromination of 2-bromodibenzofuran

Hydroxy-substituted dibenzofurans have been prepared from the bromo-derivatives by alkali fusion in the presence of a catalyst in an autoclave. The following reaction originated as an attempt to eliminate the use of an autoclave.[277] The quantities of reactants employed are similar to those used by Gilman and Van Ess.[156]

Ten grams (0.0405 mole) of 2-bromodibenzofuran, 8.5 g. of sodium hydroxide, 3.0 g. of cupric sulfate, 10 g. of copper turnings, 1 g. of copper-bronze, and 75 ml. of triethylene glycol were placed in a 250-ml., two-necked flask equipped with air condenser and motor stirrer. The reaction mixture was slowly heated, with stirring, to reflux and maintained at this temperature for 12 hours. Vacuum distillation and addition of water to the distillate yielded 3.7 g. (55%) of product melting at 75-78°. Crystallization from dilute ethanol gave 3.1 g. (45%) of dibenzofuran; m.p. and mixed m.p. with an authentic sample was 83-84°.

In a further attempt to replace the halogen atom by an hydroxyl group, kerosine was employed as the reaction medium, thus diminishing the probability of hydrogen formation. Only starting material was isolated.

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[277] H. Gilman, D. L. Esmay and R. K. Ingham, ibid., 73, 470 (1951).

Reductive debromination of 2,8-dibromodibenzofuran

Run I. A stirred mixture of 13.2 g. (0.0405 mole) of 2,8-dibromodibenzofuran, 16 g. of sodium hydroxide pellets, and 75 ml. of triethylene glycol in a two-necked flask was refluxed (240-255°) for 12 hours. The mixture was then vacuum distilled; some solid material distilled with the glycol. Addition of water to the distillate gave 3.4 g. (50%) of dibenzofuran, melting from 70-76°. One recrystallization from ethanol-water gave 3.0 g. (44%) of product melting at 83-84°. A mixed melting point with authentic dibenzofuran gave no depression.

Run II. This experiment was carried out in exactly the same manner as Run I except that the sodium hydroxide was omitted. Twelve grams (91% recovery) of 2,8-dibromodibenzofuran were thus isolated; m.p. and mixed m.p. was 191-193°.

Run III. Run I was repeated substituting absolute ethanol for the triethylene glycol. After refluxing for 12 hours, the hot solution was filtered; 11.3 g. (85.3% recovery) of cream-colored crystals were obtained and melted over the range 188-192°. One recrystallization from toluene raised the m.p. to 192-193° (mixed m.p.). On adding water to the ethanolic filtrate a very small quantity of crystals was obtained melting from 173-188°.

Run IV. Run I was repeated substituting diethylene glycol to determine the effect of a lower-boiling solvent.

After 12 hours of refluxing (195-205°), to the cooled contents additional glycol was added and the mixture vacuum distilled until the distillate yielded no solid material on dilution with water. Dilution of the distillates and filtration gave 10 g. of crude product, melting from 75-175°. This solid was first recrystallized from toluene to yield material melting from 184-190°. A second recrystallization from toluene gave 4 g. (30% recovery) of 2,8-dibromodibenzofuran, m.p. 191-193°.

The first toluene filtrate was evaporated and the resulting solid recrystallized from petroleum ether (b.p. 60-70°) to give 1 g. (10%), melting from 101-106°. Two additional recrystallizations brought the m.p. to 107.5-109°; a mixed m.p. with 2-bromodibenzofuran was not depressed.

Concentration of the petroleum ether filtrate gave a solid melting over the range 65-85°. Three recrystallizations from 95% ethanol gave 1.5 g. (22%) of dibenzofuran, m.p. and mixed m.p. 80-82°.

Nitration of 2,8-dibromodibenzofuran

Attempts to nitrate 2,8-dibromodibenzofuran with nitric acid in acetic acid or acetic anhydride were unsuccessful. A similar difficulty was encountered by Hogg[10] in attempts to nitrate 5,6-dibromohydrindene. The nitration was finally carried out in concentrated sulfuric and nitric acids.

Into a 125-ml. flask was placed 7 g. (0.022 mole) of 2,8-dibromodibenzofuran; 5 ml. of concentrated nitric acid and 10 ml. of concentrated sulfuric acid were added. Heat was evolved, but the temperature of the mixture was kept below 40-50° by cooling under the tap. The flask was then warmed for 15 minutes on a steam bath. The reaction mixture was poured upon cracked ice and the resulting crude product filtered. This solid melted over the range 170-205° and weighed 6.1 g. (75%). Two recrystallizations from glacial acetic acid raised the m.p. range to 200-226°. Recrystallization from toluene followed by two additional crystallizations from glacial acetic acid gave 0.5 g. of yellow needles melting at 332-335°. Considerable crude material melting over a wide and much lower range was obtained from the filtrates.

Anal. Calcd. for $C_{12}H_5O_3NBr_2$: Br, 43.08; for $C_{12}H_4O_5N_2Br_2$: Br, 38.42. Found: Br, 37.49, 37.61.

Preparation of 2-bromo-7-nitrodibenzofuran

Bromination of 3-nitrodibenzofuran and nitration of 2-bromodibenzofuran have been shown to yield the same product,[278] which has been proven to be the 2-bromo-7-nitro derivative;[104] the former reaction is preferable. The

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[278] N. M. Cullinane, H. G. Davey and H. J. H. Padfield, J. Chem. Soc., 716 (1934).

following is a modification of the procedure of Cullinane.[278]

In 600 ml. of glacial acetic acid was suspended 30 g. (0.14 mole) of 3-nitrodibenzofuran; to this mixture, 35 ml. of bromine was slowly added. When the bromine addition was complete, the reaction mixture was warmed to reflux temperature and there maintained for 5 hours. On heating, most of the suspended solid dissolved but soon reprecipitation occurred. On cooling and filtering, 36 g. (87%) of crude product was obtained melting over the range of 245-250°. Sohxlet extraction of the yellow solid with acetone gave 34 g. (83%) of cream-colored needles, melting at 250-251°.

Preparation of 2-bromo-7-aminodibenzofuran

2-Bromo-7-nitrodibenzofuran has been reduced by zinc and alcoholic hydrochloric acid (33% yield), and tin and concentrated hydrochloric acid (56% yield).[104] The following catalytic reduction was found more practical and gave better yields.

A suspension of 10 g. (0.034 mole) of 2-bromo-7-nitrodibenzofuran and about 2 g. of Raney nickel catalyst in 100 ml. of absolute ethanol was placed in the hydrogenation bottle. The reaction container was steam heated. The hydrogen pressure was maintained between 50 and 30 lbs./in.$^2$ After 15 minutes the pressure dropped to a constant reading. The hot solution was filtered free from catalyst and the filtrate diluted, giving 7.7 g. (87%) of the amine, melting

from 126-130.5°. One recrystallization from dilute ethanol yielded 7.2 g. (81%) of white crystals melting at 131.5-133°.

Preparation of 2-bromo-7-acetaminodibenzofuran

Seventeen grams (0.065 mole) of 2-bromo-7-aminodibenzofuran were placed in 225 ml. of benzene. The flask was warmed slightly to complete dissolution of the compound. To this solution was added 7 ml. of acetic anhydride. Within 2 minutes a flocculent white precipitate appeared. After standing for 3 hours to complete precipitation the solid was filtered and washed with petroleum ether (b.p. 28-38°). There was thus obtained 16.2 g. (81.7%) of white crystals; melting at 215-218°. Recrystallization from benzene raised the melting point to 220-220.5°.

Bromination of 2-bromo-7-acetaminodibenzofuran

To a partial solution of 10 g. (0.03 mole) of 2-bromo-7-acetaminodibenzofuran in 60 ml. of glacial acetic acid was added dropwise 5 g. (0.03 mole) of bromine. An immediate change in the crystalline form of the solid occurred and an additional 25 ml. of acetic acid was added to facilitate stirring. The mixture was warmed to 50° and stirred for 3 hours. Subsequent to cooling and filtering, there was obtained 10 g. (80%) of a light yellow solid, melting over the range 220-229°. One recrystallization from absolute ethanol gave 9.1 g. (73%) of white needles melting at 235-236°.

This was later shown to be the 2,8-dibromo-3-acetaminodibenzofuran. A mixed melting point with the product from the bromination of 2-bromo-3-acetaminodibenzofuran was greatly depressed.

Preparation of 2,8-dibromo-3-aminodibenzofuran

Eight grams of the dibromoacetamino derivative described in the preceding experiment were refluxed for 2 hours with 150 ml. of 95% ethanol and 150 ml. of concentrated hydrochloric acid. After cooling, the precipitated hydrochloride was filtered, suspended in water and decomposed with ammonium hydroxide. Filtration of the ammoniacal mixture gave 7.2 g. (93%) of a white solid, melting over the range 179-182°. Recrystallization from absolute ethanol yielded 7 g. (90%) of white needles, melting 182-183°.

Anal. Calcd. for $C_{12}H_7ONBr_2$: Br, 46.87. Found: Br, 47.02, 47.05.

Deamination of 2,8-dibromo-3-aminodibenzofuran

To a cold mixture of 9 ml. of ethanol and 2.5 ml. of concentrated sulfuric acid in a 250-ml., three-necked flask (stirrer, condenser and dropping funnel) was added 0.5 g. (0.0015 mole) of 2,8-dibromo-3-aminodibenzofuran. The mixture was cooled to 10° and a solution of 1.5 g. of sodium nitrite in 3 ml. of water was added. The temperature was not allowed to rise above 10° during this addition; the

mixture was stirred for 20 minutes after the addition to complete the reaction. The flask was then warmed cautiously until a vigorous evolution of gas began. When this reaction had moderated, the mixture was heated for 10 minutes on a steam bath. The solution was then diluted, filtered and the resulting tan solid washed well with water. This solid material melted over the range 183-188°. One recrystallization from toluene brought the m.p. to 192-193°. A mixed m.p. with authentic 2,8-dibromodibenzofuran showed no depression. The yield was 0.3 g. (55%). Thus was established the position of bromination of the 2-bromo-7-acetaminodibenzofuran.

Preparation of 2-nitrodibenzofuran

2-Nitro-3-aminodibenzofuran was prepared according to the procedure of Kirkpatrick.[110] The 2-nitro-3-acetamino derivative obtained by this procedure melted at 198-199° (196° reported by Kirkpatrick) and the 2-nitro-3-amino compound melted at 227-228° (222° reported by Kirkpatrick). An attempt to prepare the 2-nitrodibenzofuran by the method of Kirkpatrick was not successful. The deamination procedure of Bigelow, Johnson and Sandborn[279] was employed.

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[279] L. A. Bigelow, J. R. Johnson and L. T. Sandborn, Org. Syntheses, Coll. Vol. 1, 133 (1941).

To a cold mixture of 25 ml. of 25% ethanol and 5 ml. of concentrated sulfuric acid was added 6.5 g. (0.03 mole) of 2-nitro-3-aminodibenzofuran. The mixture was maintained below 10° while 3 g. of sodium nitrite in 4 ml. of water was slowly added, with stirring. This mixture was then stirred for an additional 20 minutes to complete the reaction. The flask was warmed cautiously until gas evolution had begun. When this evolution had moderated the mixture was heated for 1 hour on a steam bath. The solution was diluted and filtered, giving an orange solid melting over the range 175-195°. Two recrystallizations from methanol gave 3.5 g. (56%) of yellow needles, m.p. range 135-143°. Recrystallization from glacial acetic acid did not improve the m.p. The compound was vacuum distilled (b.p. 160-170° at 0.6 mm.) and the distillation product crystallized from methanol to yield 1.5 g. (24%) of yellow needles melting at 151-152°. A mixed m.p. with the 2-nitro derivative of Kirkpatrick (m.p. 149°) was not depressed.

Preparation of 2-bromo-8-nitrodibenzofuran

To 1 g. (0.0047 mole) of 2-nitrodibenzofuran in 20 ml. of glacial acetic acid was added dropwise 1 ml. of bromine. The solution was then refluxed for 6 hours. After cooling, the solution was diluted with water and the resulting solid filtered. This solid was recrystallized from acetone-water, giving 1.3 g. of yellow solid, melting over the range

185-203° (96% crude yield). A second recrystallization from this solvent did not improve the m.p. Recrystallization from a large amount of petroleum ether (b.p. 77-115°) gave 1 g. (74%) of yellow needles melting at 210-212°.

Anal. Calcd. for $C_{12}H_6O_3NBr$: Br, 27.38. Found: Br, 27.35, 27.30.

The only report of this compound in the literature is that of Yamashiro,[103] who gives the m.p. as 226-227°.

Preparation of 3-cyanodibenzofuran

The cuprous chloride solution was prepared from 46 g. of cupric sulfate according to Marvel and McElvain.[280] From this solution was prepared the cuprous cyanide solution by the procedure of Clarke and Read.[281]

To 27.6 g. (0.15 mole) of 3-aminodibenzofuran mixed with 45 ml. of 30% hydrochloric acid was added enough ice to bring the temperature to 0°. A solution of 10.5 g. of sodium nitrite in 30 ml. of water was then added, with stirring, while the temperature was maintained between 0-5°. Following the nitrite addition, the mixture was cautiously neutralized with sodium carbonate. The above cuprous

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[280] C. S. Marvel and S. M. McElvain, ibid., Coll. Vol. 1, 170 (1941).

[281] H. T. Clarke and R. R. Read, ibid., Coll. Vol. 1, 514 (1941).

cyanide solution was chilled and 100 ml. of toluene added to the surface. To this cyanide-toluene mixture was added the cold diazonium solution, the temperature being maintained between 0-5°. A brown oil separated. On warming, the oil dissolved in the toluene layer (an additional 75 ml. of toluene having been added) and the two layers became well defined. The layers were separated and, on cooling, no precipitate resulted in the toluene layer. The toluene solution was concentrated to about 40 ml. and again cooled, giving a red-brown precipitate. Two recrystallizations from glacial acetic acid gave 12 g. (41%) of crude product melting over the range 109-116°. Additional recrystallization did not improve the m.p.

Preparation of 3-dibenzofurancarboxylic acid

The above crude 3-cyanodibenzofuran was hydrolyzed by refluxing with 100 ml. of methanol and 20 g. of potassium hydroxide for 24 hours. This mixture was then added to 200 ml. of water; the filtrate was heated, treated with Norit-A and filtered. This filtrate was cooled with an ice bath and slowly neutralized with hydrochloric acid, yielding 7.4 g. (56%, based on the crude nitrile employed) of a brown solid. Two recrystallizations from ethanol (Norit-A) gave 5.0 g. (38%) of white solid, melting at 270-272°. Borsche and Bothe[134] similarly obtained the 3-acid, m.p. 266°, but did

not report the yield. The above m.p. agrees with that of Gilman, Smith and Cheney[202] and of Bradley.[132]

Metalation of 3-aminodibenzofuran

The procedure employed with the metalation of aniline by Gilman, Brown, Webb and Spatz[282] was followed.

3-Aminodibenzofuran (5 g., 0.027 mole) in 250 ml. of anhydrous ether was added to a 500-ml., four-necked flask fitted with stirrer, reflux condenser and dropping funnel. The system was swept with nitrogen and maintained under a nitrogen atmosphere during the reaction. To the ethereal solution was added dropwise 0.09 mole of n-butyllithium.[283] On the initial addition the solution turned black; when about 0.03 mole had been added, the color became red-brown and remained thus throughout the addition. The mixture was refluxed until Color Test II[284] became negative (32 hours). During this period the coloration slowly changed to an orange hue. Following carbonation with an ether-Dry Ice slurry and acidification with 5% hydrochloric acid, the ether layer was separated. The aqueous layer was washed

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[282] H. Gilman, G. E. Brown, F. J. Webb and S. M. Spatz, J. Am. Chem. Soc., 62, 977 (1940).

[283] H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, ibid., 71, 1499 (1949).

[284] H. Gilman and J. Swiss, ibid., 62, 1847 (1940).

with two additional portions of ether. The combined ether extracts were treated with an 8% sodium bicarbonate solution and after separation, the bicarbonate layer was warmed on a steam bath to remove any dissolved ether. This solution was then cooled in an ice bath and acidified with dilute hydrochloric acid. A brown, gummy precipitate resulted and was filtered. The original ethereal solution was extracted with 10% sodium hydroxide; acidification of this extract gave no precipitate (slight turbidity).

The brown gummy solid was digested with hot dioxane, filtered and cooled; the addition of petroleum ether (b.p. 28-38°) gave 0.5 g. of tan solid, melting from 235-245°. The solid was not soluble in most of the common solvents. Recrystallization from a dioxane-petroleum ether (b.p. 28-38°) solution did not improve the m.p.

Preparation of 4-aminodibenzofuran

A procedure for the preparation of 4-aminodibenzofuran *via* metalation and reaction with O-methylhydroxylamine appears in the Doctoral Dissertation of Willis,[8] but has not been published elsewhere. The following is a modification of that procedure.

To a solution of 42 g. (0.25 mole) of dibenzofuran in 150 ml. of anhydrous ether was added 0.4 mole of *n*-butyllithium.[283] The solution was stirred at room temperature for 38 hours; at the end of this period, Color Test II[284]

was still positive. To this solution (cooled in a salt-ice bath) was added slowly 6.1 g. (0.13 mole) of O-methylhydroxylamine in 40 ml. of ether. The free amine was prepared from O-methylhydroxylamine hydrochloride (Eastman Kodak, White Label) by treatment with 50% sodium hydroxide, the resulting vapors being passed over pellets of potassium hydroxide in a heated U-tube and subsequently condensed. Soon after the addition of the base, Color Test I[285] became negative. The solution was stirred an additional 2 hours and then hydrolyzed slowly with iced water. The ethereal layer was separated and the aqueous solution extracted twice with ether. The combined extracts were dried over sodium sulfate and the ethereal solution subsequently treated with dry hydrogen chloride to precipitate the amine hydrochloride. The 4-aminodibenzofuran hydrochloride was dissolved in 1 liter of water and the solution made alkaline. The tan amine was filtered; the yield was 12.9 g. (54%, based on the O-methylhydroxylamine of 79%, based on the amount of dibenzofuran used), melting at 83-84°. Willis obtained 21.3 g. (m.p. 81-83°) from 0.5 mole of dibenzofuran.

Preparation of 3-nitrodibenzofuran from 3-aminodibenzofuran

Hodgson and Marsden[286] have reported good yields in

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[285] H. Gilman and F. Schulze, ibid., 47, 2002 (1925).

[286] H. H. Hodgson and E. Marsden, J. Chem. Soc., 22 (1944).

replacement of an aromatic amino group by a nitro group. It was thought that this might be an excellent route to otherwise difficultly obtainable nitrodibenzofurans.

Thirteen milliliters of concentrated hydrochloric acid, 8 ml. of water and 9.2 g. (0.05 mole) of 3-aminodibenzofuran were placed in the reaction flask and cooled in a salt-ice bath. To this mixture was slowly added 4 g. of sodium nitrite in 10 ml. of water. The solution was then carefully neutralized with calcium carbonate and filtered. Into the filtrate was stirred 8.0 g. of finely powdered sodium cobaltinitrite, and the resulting crystalline diazonium salt filtered off. The diazonium cobaltinitrite (still wet) was added portion-wise, at room temperature, to a well stirred solution of 5 g. of sodium nitrite and 5 g. of cupric sulfate in 40 ml. of water in which 3 g. of cupric oxide was suspended. This mixture was stirred overnight and filtered. The residue was refluxed with portions of glacial acetic acid and filtered. The combined filtrates were concentrated to about 100 ml. and cooled to allow crystallization of the 3-nitrodibenzofuran. There was thus obtained 7.6 g. (71%) of crude product melting from 140-152°. Two recrystallizations from glacial acetic acid brought the m.p. range to 165-179°. An additional recrystallization from absolute ethanol and finally again from glacial acetic acid brought the m.p. to 181-182°; the final yield was 3.3 g.

(31%). A mixed m.p. with authentic 3-nitrodibenzofuran was not depressed.

Preparation of 4-nitrodibenzofuran from 4-aminodibenzofuran

A procedure similar to that of the previous experiment was employed for the preparation of 4-nitrodibenzofuran.

Into the reaction flask were placed 9 ml. of hydrochloric acid, 5 ml. of water and 6.1 g. (0.0333 mole) of 4-aminodibenzofuran; this mixture was cooled in a salt-ice bath. Sodium nitrite (2.5 g.) in 10 ml. of water was slowly added. The diazonium cobaltinitrite was prepared and decomposed as above. Recrystallization from dilute ethanol gave a yellow solid, melting from 60-90°; further recrystallization from this solvent did not improve the m.p. One recrystallization from petroleum ether (b.p. 77-115°) raised the m.p. range to 132-136°; two additional recrystallizations gave tan needles melting at 138-139°. The final yield was 1.5 g. (21%); in a second run, eliminating the ethanolic recrystallization, a 28% yield was obtained.

Preparation of 2-chloromethyldibenzofuran

The preparation of 2-chloromethyldibenzofuran has been reported by Kirkpatrick.[110] The following are attempts to repeat the preparation of this compound.

Run I. To a partial solution of 84 g. (0.5 mole) of dibenzofuran in 300 ml. of glacial acetic acid in a

three-necked flask (stirrer, thermometer and gas delivery tube) was added 25 g. (0.27 mole) of trioxymethylene and 20 g. of freshly fused zinc chloride. Gaseous hydrogen chloride was bubbled into the vigorously stirred solution. After about 40 minutes the temperature began to rise and complete solution occurred. The solution was cooled to 25° and kept at this temperature for 3 hours while additional hydrogen chloride gas was passed through. A precipitate slowly formed. Filtration gave 30.3 g. of recovered dibenzofuran, m.p. and mixed m.p. 77-82°. Dilution of the filtrate with iced water gave an additional 44.5 g. of dibenzofuran (89% total recovery).

Run II. The reaction set-up and quantities employed were the same as with Run I. The reaction was run as previously except for not cooling to room temperature. The temperature in the flask rose to 55° without external heating, but soon began to fall. The solution was then warmed to keep the internal temperature at 55°. Hydrogen chloride gas was bubbled through for 5 hours at this temperature. The reaction mixture was then poured upon ice, yielding a gummy liquid. Attempts to recrystallize this liquid (Kirkpatrick gave m.p. as 78.5-79.5°) from several solvents all resulted in "oiling out" of the solute. The product was extracted with ether, the ether extract then being washed with a sodium carbonate solution and dried over sodium sulfate. The solvent was distilled off and the

residue subjected to vacuum distillation. Under a pressure of 0.2 mm, with a bath temperature of 150-170°, a green polymer was formed with the evolution of considerable hydrogen chloride gas. A small amount of dibenzofuran (mixed m.p.) sublimed on the condenser. On cooling, the green material solidified; pulverization gave a light green powder melting from 92-110°. Two recrystallizations of a portion from methyl cellosolve gave a light yellow solid, melting at 123-126°.

Run III. This reaction was run as previously except carbon tetrachloride was employed as a solvent (rather than acetic acid, which might have taken part in affecting polymerization). The mixture warmed slightly on reaction, but required external heating to maintain the temperature at 55°; hydrogen chloride was passed through the solution at this temperature for 8 hours. The carbon tetrachloride solution was filtered, washed with sodium carbonate solution and the solvent distilled off. Vacuum distillation of the residue (0.5 mm) gave the usual green polymer.

Run IV. Run III was repeated with the exception that the product was chromatographed on a 6 inch column of 150 g. of adsorption alumina (Fisher) rather than vacuum distilled. The column was eluted with carbon tetrachloride, petroleum ether (b.p. 60-70°) and finally with benzene, the eluates being collected in 50 ml. portions. Evaporation of the solvent from the chromatographed solutions gave yellow

oils which defied crystallization attempts.

Similar difficulties in obtaining a pure product were encountered by R. G. Johnson in the preparation of the 2-chloromethyldibenzofuran and by G. R. Wilder in the preparation of the 2-chloromethyldibenzothiophene.

## Dibenzothiophene Derivatives

### Preparation of 2-bromodibenzothiophene

Courtot, Nicolas and Liang[287] were the first to report the preparation of 2-bromodibenzothiophene; however experimental details were not given. Cullinane, Davies and Davies[288] prepared the 2-bromo derivative from 2-aminodibenzothiophene and by direct bromination. The following is a modification of the procedure of Jacoby (Doctoral Dissertation)[11] which has not been published elsewhere.

In 130 ml. of carbon tetrachloride was dissolved 73.6 g. (0.4 mole) of dibenzothiophene (Eastman Kodak, White Label) and a very small quantity of aluminum trichloride was added. While the solution was stirred and warmed, 64 g. (0.4 mole) of bromine was added dropwise (2.5 hours required).

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[287] C. Courtot, L. Nicolas and T. H. Liang, Compt. rend., 186, 1624 (1928).

[288] N. M. Cullinane, C. G. Davies and G. I. Davies, J. Chem. Soc., 1435 (1936).

The solution was exposed to ultraviolet radiation while heating and stirring were continued for 24 hours. After cooling, the bromine and carbon tetrachloride were removed by distillation (washing with bisulfite and drying over sodium sulfate were found to be unnecessary steps). Vacuum distillation of the residue (main fraction boiling from 145-155° at 0.1 mm.) gave 70 g. (67.5%) of crude product, melting from 90-110°. Three recrystallizations from absolute ethanol (Jacoby did not specify a recrystallization solvent) gave 55 g. (52.5%) of product melting at 126-127°. The m.p. range after one recrystallization was 110-115°; after the second, 118-125°; after the third, 126-127°. Jacoby obtained 54% of product melting at 124-125°. An additional 12 g. of impure material was recovered by concentration of the filtrates.

Preparation of 2-bromodibenzothiophene-5-dioxide

The preparation of 2-bromodibenzothiophene-5-dioxide has been reported by Courtot,[289] the compound being obtained by oxidation with potassium dichromate of 2-bromodibenzothiophene; however, no experimental details were given. The only other report is that of Muth and Putzer,[290] who report

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[289] C. Courtot, Compt. rend., 198, 2260 (1934).

[290] F. Muth and B. Putzer, PBL 63936. (Enlargement Print of Frames 1004-10.0 of FIAT microfilm Reel C 60, PB 17657.) March 1933. 7 pp. Photo. Ger. 5, p. 568a, #7, May 16, 1947.

chromic acid oxidation of 2-bromodibenzothiophene to yield the -5-dioxide, m.p. 256°. The following procedure is easily carried out and gives good yields.

Fifteen grams (0.058 mole) of 2-bromodibenzothiophene were suspended in 200 ml. of glacial acetic acid. To this solution was slowly added 30 ml. of 30% hydrogen peroxide, and the mixture was then slowly warmed to reflux temperature. On warming, the solid entirely dissolved and reprecipitation began shortly thereafter. The mixture was refluxed for 1 hour, cooled, filtered and the precipitate washed well with water. The white sulfone melted at 261-262° and weighed 16 g. (93.5%). Courtot reports a m.p. of 266-267°; Muth and Putzer report a m.p. of 256°. After digestion with absolute ethanol the 2-bromodibenzothiophene-5-dioxide melted at 261.5-262°.

Preparation of 2-bromo-7-nitrodibenzothiophene-5-dioxide

A search of the literature revealed no reports of the nitration of 2-bromodibenzothiophene-5-dioxide or the preparation of 2-bromo-7-nitrodibenzothiophene-5-dioxide by other means.

Into a three-necked, 250-ml. flask was placed 15 g. (0.051 mole) of 2-bromodibenzothiophene-5-dioxide. Fifty milliliters of concentrated sulfuric acid were added, forming a thick paste, and then 33 ml. of fuming nitric acid (sp. gr. 1.50) was added slowly. The stirred mixture was

warmed to 80° and there maintained for 2 hours. Upon cooling, the reaction mixture was filtered and washed well with water immediately to stop action of the concentrated acids on the filter paper; this was found to give a better product than that obtained on dilution and subsequent filtration. The crude yield was 14 g. (80%) of a light yellow solid, melting over the range from 250-300°. Three recrystallizations from glacial acetic acid gave 9 g. (52%) of pale yellow needles melting at 319-321°. After one recrystallization the m.p. range was 295-315°; after the second, 315-320°; and following the third, 319-321°.

Anal. Calcd. for $C_{12}H_6O_4SNBr$: S, 9.43. Found: S, 9.39, 9.39.

Preparation of 2-bromo-7-aminodibenzothiophene-5-dioxide

Run I. One gram (0.0294 mole) of 2-bromo-7-nitrodibenzothiophene-5-dioxide was suspended in 25 ml. of absolute ethanol and about 0.5 g. of Raney nickel catalyst was added. The initial hydrogen pressure was 40 lbs./in.$^2$ and the reaction bottle was steam heated. After 45 minutes, there was no noticeable drop in the hydrogen pressure. The still-warm mixture was filtered; dilution of the filtrate with water gave a red solid melting from 250-295°. The residue from the filtration was extracted with 75 ml. of hot toluene. Filtration, concentration to about 10 ml. and

cooling of the toluene solution gave, subsequent to an additional filtration, a red solid melting from 260-293°. Three recrystallizations of the combined solids from glacial acetic acid (Norit-A) raised the m.p. range to 313-318°. A mixed m.p. with starting material was not depressed. The yellow solid weighed 0.5 g. (50% recovery).

Run II. Nine grams (0.0264 mole) of 2-bromo-7-nitrodibenzothiophene-5-dioxide were suspended in 175 ml. of absolute ethanol. To this mixture were added 17 g. of granular tin and 175 ml. of concentrated hydrochloric acid. The mixture was stirred at reflux temperature for 2 hours. Complete solution did not occur; however the suspended precipitate soon changed in coloration from yellow to white. The amine hydrochloride (m.p. about 320°, with decomposition) was filtered, suspended in water and decomposed with ammonium hydroxide. There was thus obtained 7 g. of yellow solid, melting from 315-320°. A mixed m.p. with starting material was greatly depressed. Two recrystallizations from acetone-methanol gave 5.5 g. (67%) of a yellow solid (Norit-A did not lessen the intensity of the yellow coloration), melting at 331-333°, with some decomposition.

Anal. Calcd. for $C_{12}H_8O_2SNBr$: Br, 25.77. Found: Br, 25.47, 25.54.

Preparation of 2-nitrodibenzothiophene

The nitration of dibenzothiophene was reported in two

papers by Courtot and co-workers[287,291] but no experimental details were given. Cullinane and co-workers[288] reported a 40% yield of 2-nitrodibenzothiophene by nitration of dibenzothiophene with fuming nitric acid; however, Gilman and Nobis[292] were unable to duplicate the yield, usually obtaining less than 20%. The procedure of Cullinane was also followed during the course of this investigation, a 23% yield being obtained. The procedure which follows is a modification of the procedure of Gilman and Nobis.[292]

To 40 g. (0.218 mole) of dibenzothiophene in 300 ml. of glacial acetic acid was slowly added 40 ml. of fuming nitric acid (sp. gr. 1.50). The solution was maintained between 25-30° during this addition (1 hour required). When the addition was complete, the reaction mixture was stirred for 2 hours at room temperature. The mixture was filtered and dried on a Buchner funnel (without washing with water). The nitration product was digested for 2 hours with 250 ml. of refluxing ethanol to remove the soluble 2-nitrodibenzothiophene-5-oxide. The insoluble 2-nitrodibenzothiophene was removed by filtration of the hot solution, giving 18 g., melting at 180-186°. Recrystallization from a benzene-petroleum ether (b.p. 77-115°) solution gave 15 g. of yellow

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[291] C. Courtot and C. Pomonis, Compt. rend., 182, 893 (1926).

[292] H. Gilman and J. F. Nobis, J. Am. Chem. Soc., 71, 274 (1949).

needles (30%), melting at 187-188°. Nobis obtained a 28.2% yield, melting at 186-187°, no recrystallization being reported.

Preparation of 2-acetaminodibenzothiophene

Courtot and Pomonis[293] first prepared 2-acetaminodibenzothiophene, but experimental details were not included in their report. Gilman and Jacoby[294] prepared this compound in a manner similar to that described below, but gave no yield. The 2-aminodibenzothiophene was prepared in an 87% yield by catalytic reduction of the 2-nitro derivative according to the procedure of Gilman and Nobis.[292]

To a solution of 9 g. (0.0452 mole) of 2-aminodibenzothiophene in 200 ml. of benzene was added 9 ml. of acetic anhydride. Within 5 minutes a heavy white precipitate was formed; the mixture was allowed to stand for 1 hour to complete the reaction and then filtered. The solid thus obtained melted at 176-178°. One recrystallization from benzene gave 10 g. (92%) of white needles, melting at 178-179°. Further recrystallization did not change the m.p. The melting point reported by Courtot and Pomonis was 168°; that of Gilman and Jacoby, 178°; and a m.p. of 181-183°

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293 C. Courtot and C. Pomonis, Compt. rend., 182, 931 (1926).

294 H. Gilman and A. L. Jacoby, J. Org. Chem., 3, 108 (1938).

(prepared by Beckmann rearrangement of the 2-acetyl oxime) was reported by Burger, Wartman and Lutz.[295]

Nitration of 2-acetaminodibenzothiophene

This reaction has been reported by Gilman and Jacoby.[294] 2-Acetaminodibenzothiophene (7 g., 0.038 mole) was dissolved in 300 ml. of glacial acetic acid. With stirring, 6 ml. of fuming nitric acid (sp. gr. 1.50) was added, keeping the temperature at 25°; precipitation soon began. The mixture was stirred at room temperature for 1 hour and filtered directly. The product was washed well with water and dried to give 4 g. of yellow crystals, melting at 208-209°. Dilution of the filtrate gave an additional 3.2 g. melting from 200-205°. Recrystallization of this material from methanol brought the m.p. to 208-209°. The total yield of pure compound was 6.1 g. (72%) (Gilman and Jacoby reported a 67% yield).

Nitration of 2-acetaminodibenzofuran has been shown to give the 2-acetamino-3-nitro derivative;[104] however, infrared absorption measurements of the above nitro-2-acetamino compound indicate that the nitro group is not on the same ring as the acetamino grouping. For additional consideration of this and the following reaction, see the Discussion section.

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[295] A. Burger, W. B. Wartman and R. E. Lutz, J. Am. Chem. Soc., 60, 268 (1938).

Attempted hydrolysis of nitro-2-acetaminodibenzothiophene

This reaction was reported by Gilman and Jacoby[294] to give a nitrogen-free compound melting at 88°. Hydrolysis of 2-acetamino-3-nitrodibenzofuran proceeds normally giving the nitro-amine.[104] The following is additional information which may be helpful in establishing the identity of the hydrolysis product.

Run I. A mixture of 0.5 g. (0.002 mole) of the nitro-acetamino compound with 20 ml. of absolute ethanol and 20 ml. of concentrated hydrochloric acid was refluxed for 2 hours. The solid material all dissolved, but the solution soon became turbid and a brown oil separated. Dilution of the reaction mixture with water and cooling gave a brown solid, melting from 70-80°. Suspension of the solid in water and treatment with ammonium hydroxide did not change the m.p. Recrystallization from dilute methanol gave a white solid melting at 85-87°; a second recrystallization from glacial acetic acid raised the m.p. to 88-89°. The yield of white needles was 0.2 g.

Run II. To determine the effect of the hydrochloric acid, hydrolysis was attempted using 50% sulfuric acid; only a black charred substance was obtained; the substance defied purification attempts.

Run III. Run I was repeated, the reaction being stopped by dilution with water as soon as all of the solid

had dissolved. The resulting yellow solid was filtered and washed with water; the m.p. range was 71-84°. Two recrystallizations from glacial acetic acid gave white needles, melting at 87-87.5° (0.23 g.).

This anomalous product (1-chlorodibenzothiophene) is insoluble in 20% sodium hydroxide and soluble in benzene. A Beilstein halogen test was negative. The compound burns with a smoky flame. A mixed m.p. with dibenzothiophene melted from 60-75°. Qualitative alkali fusion tests for nitrogen [redacted] were negative. A mixed m.p. with a sample of Jacoby's compound was not depressed. A Rast determination indicates the molecular weight of the substance to be about ~~163~~ (220).

Preparation of 2-bromo-8-nitrodibenzothiophene

The preparation of 2-bromo-8-nitrodibenzothiophene is reported in two papers by Courtot and co-workers[287,296] but the yield and experimental details are lacking.

Ten grams (0.038 mole) of 2-bromodibenzothiophene were partially dissolved in 100 ml. of glacial acetic acid and 15 ml. of fuming nitric acid (sp. gr. 1.50) added dropwise. No noticeable change occurred; the reaction mixture was warmed to 50° and the suspended solid slowly turned yellow. The mixture was stirred at this temperature for 1.5 hours

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[296] C. Courtot and C. Pomonis, Compt. rend., 198, 2003 (1934).

and then filtered directly. There was thus obtained 10 g. of solid melting from 160-200°. Recrystallization from glacial acetic acid raised the m.p. range to 170-207°. The product was digested for 2 hours with refluxing ethanol and then again recrystallized from glacial acetic acid; the m.p. range was 233-242°. Two additional recrystallizations from this solvent gave 3 g. (25.5%) of pale yellow needles, melting at 254-256.

Preparation of 2-bromo-8-aminodibenzothiophene

Again the sole report of this compound is that of Courtot[287] who gives only the m.p., stating that the substance was obtained by reduction of the 2-bromo-8-nitro derivative, but not mentioning the method of reduction or any details.

To a suspension of 2.5 g. (0.0081 mole) of 2-bromo-8-nitrodibenzothiophene in 50 ml. of absolute ethanol was added about 0.5 g. of Raney nickel catalyst. The initial reaction pressure was 40 lbs./in.$^2$ After shaking over night, 4 lbs./in.$^2$ had been absorbed. The solution was filtered free from catalyst and diluted to give 2 g. of a light violet solid melting from 100-130°. Three recrystallizations from ethanol gave 1 g. (45%) of solid melting at 149-150°.

Preparation of dibenzothiophene-5-oxide

The oxidation of dibenzothiophene with hydrogen peroxide has been carefully reviewed and studied.[297] Several preparations of dibenzothiophene-5-oxide were run and it is believed by this author that the most practical preparation of the compound is a modification of the method of Brown, Christiansen and Sandin[298] which follows.

Fifty grams (0.272 mole) of dibenzothiophene were dissolved in 450 ml. of carbon tetrachloride; the solution was cooled to 0-5° with an ice bath and kept within the temperature range while chlorine gas was bubbled through. The treatment with chlorine was continued until 20 g. of chlorine had been absorbed. The pink coloration reported by Brown et al. did not always appear. The compound was hydrolyzed by vigorous shaking with ice and water; the hydrolysis proceeded rather slowly; therefore after much shaking the mixture was allowed to stand overnight. The pink (or white) solid thus formed was filtered and washed well with water. The crude yield was 51.3 g. (94%), melting from 170-180°. One recrystallization from benzene gave 41.5 g. (77%, the same yield obtained by Brown et al.) of

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[297] H. Gilman and D. L. Esmay, J. Am. Chem. Soc., 74, 2021 (1952).

[298] R. K. Brown, R. G. Christiansen and R. B. Sandin, ibid., 70, 1748 (1948).

white prismatic crystals, melting at 185-187°. An additional 4 g. of solid melting at 182-186° was obtained on concentration of the benzene solution.

Infrared absorption measurements indicated a small amount of the -5-dioxide to be present in the above product. A run was made following the procedure above but stopping the reaction before an equivalent of chlorine had been absorbed. The material thus obtained also showed evidence of some -5-dioxide impurity. The -5-monoxide product obtained by the procedure of Gilman and Esmay[297] was extracted several times with petroleum ether (b.p. 77-115°) and recrystallized twice from benzene, but failed to give a product without indications of the dioxide.

Reaction of dibenzothiophene-5-oxide with bromine

The following experiment was carried out in an attempt to prepare 3-bromodibenzothiophene-5-oxide.[298]

Six grams (0.03 mole) of dibenzothiophene-5-oxide were partially dissolved in 50 ml. of carbon tetrachloride, and a small amount of aluminum trichloride added. The solution was warmed and stirred while 5.0 g. (0.04 mole) of bromine was added dropwise. Stirring and heating below reflux temperature were continued for 24 hours, with no apparent evolution of hydrogen bromide. Complete solution occurred, but a precipitate was formed on cooling. The precipitate was

filtered and washed well with water. Two recrystallizations from n-butanol gave 3.7 g. (36%) of a white solid melting at 223-224°. A mixed m.p. with 2,8-dibromodibenzothiophene (m.p. 223-224°), prepared by direct bromination of dibenzothiophene, was not depressed. Infrared absorption measurements have confirmed the presence in the starting material of the sulfoxide group and its absence in the final product; also, nuclear bromo-substitution is indicated.

In another run, using only 0.5 equivalent of bromine, a 40% recovery of the starting -5-oxide plus a 28% yield of dibenzothiophene (mixed m.p.) were obtained.

Reaction of dibenzothiophene-5-oxide with hydrogen bromide

Hydrogen bromide gas was prepared and freed from bromine by the procedure of Booth[299] (using tetrahydronaphthalene and bromine). The hydrogen bromide gas was bubbled for 3 hours through a partial solution of 5 g. (0.025 mole) of dibenzothiophene-5-oxide in 50 ml. of carbon tetrachloride and warmed to 50-55°. Soon after the initial hydrogen bromide passage, the reaction mixture began to turn red-brown in color and after 1 hour had become a dark red. The suspended solid dissolved. A test for bromine with

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[299] H. S. Booth, "Inorganic Synthesis", Vol. I, McGraw-Hill Book Company, New York, 1939, p. 151.

fluorescein[300] was quite positive and a similar test of the gas before entering the reaction flask proved negative. With continued warming, the reaction solution was allowed to stand for 24 hours. On cooling, a small amount of solid was obtained, melting from 215-220°; this solid was recrystallized from n-butanol to give 0.12 g. of white crystals melting at 227-229°. A mixed m.p. with dibenzothiophene-5-dioxide melted from 226-230°.

The solvent was distilled from the carbon tetrachloride solution, leaving a white residue melting from 60-90°. Recrystallization from ethanol did not improve the m.p. The solid was then vacuum distilled (b.p. 150-160°/2-3 mm.) Five recrystallizations from ethanol gave 15 g. (33%) of material melting from 91-95°; a mixed m.p. with dibenzothiophene also melted from 91-95°.

In a repeat run, employing the same quantities, 2 g. (44%) of white needles, melting at 96-97° (mixed m.p. with dibenzothiophene not depressed), and 0.13 g. of dibenzothiophene-5-dioxide, m.p. 233° (mixed m.p.), were obtained.

Reaction of dibenzothiophene-5-oxide with N-bromosuccinimide

An additional attempt was made to prepare 3-bromodibenzothiophene-5-oxide employing N-bromosuccinimide. The

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300 F. Feigl, "Qualitative Analysis by Spot Tests", Elsevier Publishing Company, New York, 1946, p. 194.

procedure used was based on that of Buu-Hoi and Royer[120] for the bromination of dibenzothiophene.

Ten grams (0.05 mole) of dibenzothiophene-5-oxide, 20 g. of N-bromosuccinimide and 100 ml. of carbon tetrachloride were placed in a three-necked flask fitted with a stirrer and condenser. A small amount of aluminum trichloride was added and the solution brought to reflux temperature. The reaction mixture was exposed to ultraviolet light and, with stirring, refluxed for 48 hours. The mixture was then filtered, washed with dilute sodium hydroxide and subsequently with water. The residue weighed 9 g. and melted from 152-168°. Two recrystallizations from benzene gave 6.5 g. (65% recovery) of the starting -5-oxide, melting at 184-186° (mixed m.p.).

Evaporation of the carbon tetrachloride solution left a residue melting from 50-95°. Recrystallization from dilute ethanol gave a white solid which partially melted from 85-90°, but did not completely melt until a temperature of 158° was reached. Attempts to further purify this solid by recrystallization were unsuccessful.

Preparation of 3-aminodibenzothiophene

Dibenzothiophene-5-oxide was nitrated by a procedure based upon that of Gilman and Jacoby[294] for the nitration of the dioxide.

Fifteen grams of dibenzothiophene-5-oxide (0.075 mole), 33 ml. of glacial acetic acid and 33 ml. of concentrated sulfuric acid were placed in the reaction flask and the mixture cooled in an ice bath. To the stirred mixture was added 36 ml. of fuming nitric acid (sp. gr. 1.50) over a period of 20 minutes. Complete solution resulted. After standing for 30 minutes at 0-5°, the solution was poured upon 200 g. of cracked ice. A light yellow, gummy solid was formed which hardened within 1 hour. The solid was filtered and washed well with water. The crude material weighed 16 g. (87%) and melted from 203-207°. One recrystallization from absolute ethanol gave 13.5 g. (73.5%) of 3-nitrodibenzothiophene-5-oxide (white platelets) melting at 210-211°. (Brown et al.[298] obtained a 74% yield of product melting from 209.5-210.5°.)

The 3-nitrodibenzothiophene-5-oxide was reduced to 3-aminodibenzothiophene by the procedure of Brown and coworkers.[298] A 74% yield of the cream-colored amine was obtained melting at 121-122°.

Preparation of 3-bromodibenzothiophene

From 3-aminodibenzothiophene. A procedure for the preparation of the 3-~~amine~~ bromo from the 3-~~bromo~~ amino derivative has been reported by Illuminati, Nobis and Gilman.[301]

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[301] G. Illuminati, J. F. Nobis and H. Gilman, J. Am. Chem. Soc., 73, 5887 (1951).

The cuprous bromide was freshly prepared by the procedure of Vogel.[302] The nitrosyl sulfuric acid was prepared by the method of Hodgson and Walker.[303]

Six grams (0.03 mole) of 3-aminodibenzothiophene were dissolved in 70 ml. of glacial acetic acid. The solution was cooled to room temperature and slowly added to a well-stirred solution of nitrosyl sulfuric acid (10% excess of sodium nitrite employed) in an ice bath. This diazonium solution was then added to a solution of cuprous bromide (0.03 mole) in 125 ml. of 48% hydrobromic acid and the resulting purplish-black solution refluxed for 1 hour. The cooled mixture was then poured into a large volume of water and the brown precipitate so obtained was filtered off.

Illuminati's procedure calls for a thorough extraction of the product with ether; however, the residue was found to be quite soluble in this solvent. The ether was evaporated and the residue dissolved in hot ethanol (Norit-A); filtration and dilution with water of the cooled filtrate gave 4.9 g. (62%) of light brown platelets, melting from 82-91°. Two recrystallizations from ethanol gave 3.1 g. (39%),of product melting from 93-96°.

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[302] A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Company, New York, 1948, p. 187.

[303] H. H. Hodgson and J. Walker, J. Chem. Soc., 1620 (1933).

From 3-bromodibenzothiophene-5-dioxide. The reduction of dibenzothiophene-5-dioxide with lithium aluminum hydride has been reported by Bordwell and McKellin.[304] The 3-bromodibenzothiophene-5-dioxide sample was prepared by H. A. Pacevitz.[305]

3-Bromodibenzothiophene-5-dioxide (0.5 g., 0.0017 mole) and 0.2 g. (0.005 mole) of lithium aluminum hydride were placed in a 250-ml., three-necked flask and 100 ml. of anhydrous ether was added. The reaction mixture was refluxed for 1.5 hours, with stirring. The cooled mixture was then hydrolyzed by the dropwise addition of water. Dilute hydrochloric acid was then added to dissolve the resulting precipitate; the layers were separated and the aqueous layer was extracted twice with ether. The combined ether solutions were evaporated, leaving a light yellow gum. The residue was extracted with hot ethanol; dilution with water of the ethanolic extract gave a white solid melting from 40-63°. Three recrystallizations from absolute ethanol gave 0.2 g. (44.5%) of white needles melting at 98-99°. A mixed m.p. with the 3-bromodibenzothiophene prepared from 3-aminodibenzothiophene was not depressed.

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[304] F. G. Bordwell and W. H. McKellin, J. Am. Chem. Soc., 73, 2251 (1951).

[305] H. Gilman, A. L. Jacoby and H. A. Pacevitz, J. Org. Chem., 3, 120 (1938).

Preparation of 4-aminodibenzothiophene

The procedure of Gilman and Avakian[306] was followed for this preparation; however a 45% yield, rather than the 64% yield reported, was obtained. D. L. Esmay[307] has also reported obtaining a much lower yield by this procedure.

The reaction was repeated employing the same quantities as in the report of Gilman and Jacoby with the exception of the amount of O-methylhydroxylamine used. After the addition of the reported 10 g. (0.21 mole) of the amine, Color Test I remained positive; 3 additional g. of the amine was added before the Color Test became negative. The product was purified as reported except that petroleum ether (b.p. 77-115°) was employed as the recrystallization solvent rather than methanol. There was thus obtained 27.2 g. (67%) of 4-aminodibenzothiophene.

Preparation of 4-(β-dimethylaminoethylamino)-dibenzothiophene

A mixture of 6.5 g. (0.032 mole) of 4-aminodibenzothiophene and 7.15 g. (0.05 mole) of β-dimethylaminoethyl chloride hydrochloride (Matheson) was heated (under nitrogen) at 150-155° for 4 hours. After cooling, the reaction mixture was dissolved in hot water, cooled, and filtered

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[306] H. Gilman and S. Avakian, J. Am. Chem. Soc., 68, 1514 (1946).

[307] D. L. Esmay, unpublished studies.

free from a small amount of insoluble material. The acidic solution was made basic with ammonium hydroxide and extracted with ether. The ethereal extract was dried over sodium sulfate and the solvent subsequently removed. Vacuum distillation of the residue gave 6.1 g. (71%) of a light yellow liquid, b.p. 221-224°/0.5 mm.

Anal. Calcd. for $C_{16}H_{18}N_2S$: S, 11.86. Found: S, 11.84, 11.75.

Preparation of 4-(β-dimethylaminoisopropylamino)-dibenzothiophene

A mixture of 6.5 g. (0.032 mole) of 4-aminodibenzothiophene and 7.9 g. (0.05 mole) of β-dimethylaminoisopropyl chloride hydrochloride (Matheson) was heated, under nitrogen and with stirring, at 155-160° for 5 hours. After cooling, the reaction mixture was treated with 600 ml. of hot water and filtered free from insoluble material. This filtrate was then made basic with ammonium hydroxide and subsequently extracted with anhydrous ether. The ethereal extract was dried over sodium sulfate and the ether then evaporated. The residual oil was vacuum distilled, yielding 4.9 g. (54%) of a yellow oil, b.p. 215-218°/0.3 mm. The compound tends to become discolored on standing and was redistilled for analysis.

Anal. Calcd. for $C_{17}H_{20}N_2S$: S, 11.26. Found: S, 11.22, 11.15.

## Nitrogen Heterocyclic Derivatives

### Reaction of phenothiazine with lithium

D. L. Esmay[308] reacted dibenzofuran with lithium in a dioxane medium and obtained a 77.2% yield of o-hydroxydiphenyl; under similar reaction conditions with dibenzothiophene a 21.4% yield of diphenyl, 18.3% of o-mercaptodiphenyl and 48.8% recovery of dibenzothiophene were obtained. Studies of this lithium cleavage reaction is herein extended to phenothiazine, 10-ethylphenothiazine and carbazole.

Run I. Purification of the dioxane employed was effected by the procedure of Fieser.[309] To 200 ml. of purified dioxane in a three-necked flask (condenser, stirrer and nitrogen atmosphere) were added 19.9 g. (0.1 mole) of phenothiazine and 2.22 g. (0.32 g. atom) of lithium. The mixture was heated to reflux temperature and there maintained for 15 hours. The odor of hydrogen sulfide was evident and a lead acetate test for this substance was positive soon after heating was begun. Color Tests I, taken initially and at intermittent points, were negative. The color at the start was a dark red, gradually becoming lighter as refluxing was

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[308] H. Gilman and D. L. Esmay, J. Am. Chem. Soc., 75, in press (1953).

[309] L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, New York, 1941, p. 368.

continued. At the end of the 15-hour period, a small amount of lithium remained. The reaction mixture was cooled and slowly hydrolyzed with a water-dioxane solution. The solvent was distilled off at water pump pressure, leaving a light brown, gummy solid. The residue was extracted with two portions of 5% sodium hydroxide (50 ml. each). The remaining residue was washed with water and then extracted with 5% hydrochloric acid (two 50-ml. portions). The residue from the acid treatment was extracted with two 25-ml. portions of methanol.

Neutralization of the sodium hydroxide solution gave a yellow-brown oil (mercaptan odor). The oil was dissolved in ether and the ethereal solution extracted with 5% sodium hydroxide. Slow neutralization of the basic solution, while keeping the temperature at 0-5°, gave 5.8 g. (29%) of a yellow solid, melting at 35-37°. On standing the solid changed to an oil again, probably due to some oxidation to the disulfide. The mercaptan was dissolved in dilute sodium hydroxide and an alcoholic solution of iodine added until coloration due to iodine was evident. Filtration gave the disulfide of o-mercaptodiphenylamine, melting at 161-162°. A m.p. of 162° for this disulfide is reported by Kiptrianov and Ushenko.[310]

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[310] A. I. Kiprianov and I. K. Ushenko, J. Gen. Chem. (U.S.S.R.), 17, 2201 (1947) [C. A., 42, 5016 (1948)].

Anal. Calcd. for $C_{24}H_{20}N_2S_2$: S, 16.02. Found: S, 15.92, 15.81. Neutralization of the hydrochloric acid solution gave no solid material (slight turbidity).

Water dilution of the methanolic extract gave a light yellow solid which melted from 45-50°. Recrystallization from dilute ethanol gave 0.74 g. (4.4%) of diphenylamine (mixed m.p.), melting at 51-52°.

Two recrystallizations from toluene of the residue remaining after the methanolic extraction gave 7.2 g. (36% recovery) of light yellow solid, melting at 178-180°; a mixed m.p. with the starting phenothiazine was not depressed.

Run II. Run I was repeated, except the solution was carbonated rather than hydrolyzed. The reaction was worked up by the normal procedure following carbonation. No acid was obtained from the bicarbonate solution. Neutralization of the sodium hydroxide extract gave 6.7 g. of o-mercapto-diphenylamine, melting at 35-37° (a mixed m.p. with a sample from Run I was not depressed). No diphenylamine was isolated. By the methods of Run I, 7.9 g. (37.2% recovery) of starting phenothiazine (mixed m.p.) was obtained, melting at 180-181°.

Run III. Run I was repeated employing anhydrous ether as a solvent rather than dioxane. The only material isolated was 16 g. (80.5% recovery) of phenothiazine, melting (after one recrystallization from toluene) at 178-181°.

Reaction of 10-ethylphenothiazine with lithium

Run I. 10-Ethylphenothiazine (11.2 g., 0.05 mole), 0.8 g. of lithium (0.115 g. atom) and 100 ml. of purified dioxane were placed in a three-necked flask fitted with stirrer and reflux condenser and under a nitrogen atmosphere. The mixture was refluxed for 15 hours. Color Tests I were negative throughout the reaction. The reaction mixture was cooled and carbonated upon an ether-Dry Ice slurry. The resulting mixture was acidified with 5% hydrochloric acid and the layers separated; the aqueous layer was washed with additional ether. The ether layer was then extracted with an 8% sodium bicarbonate solution; the bicarbonate extract was warmed on a steam bath to remove dissolved ether. The solution was cooled in an ice bath and carefully acidified with dilute hydrochloric acid. No product separated on neutralization.

The ethereal solution was then extracted with 10% sodium hydroxide. Neutralization gave a yellow-brown oil. The yield was 2.7 g. (24%, if the product was o-mercaptodiphenylethylamine). Attempts to prepare the disulfide gave a tan gummy material which defied purification.

The original aqueous acidic solution on neutralization with dilute sodium hydroxide gave no precipitate.

The ethereal solution (after sodium hydroxide extraction) was evaporated. The residue was recrystallized thrice

from absolute ethanol to give 3.5 g. (30.7% recovery) of 10-ethylphenothiazine, melting at 100-102° (mixed m.p.).

Run II. The procedure of Run I was followed with the exception that 0.23 g. atom of lithium was employed rather than 0.115 g. atom. The product was worked up as before and there were thereby obtained 3.7 g. (33%) of the mercaptan and 3.2 g. (28.6% recovery) of 10-ethylphenothiazine. No diphenylethylamine was isolated from the reaction.

Reaction of carbazole with lithium

The set up for this reaction was the same as for the reaction of phenothiazine with lithium. Carbazole (16.7 g., 0.1 mole), 2.2 g. (0.32 g. atom) of lithium and 200 ml. of purified dioxane were employed. The reaction mixture was refluxed for 24 hours. Intermittent Color Tests I were negative. The mixture was filtered through glass wool upon an ether-Dry Ice slurry. The reaction was worked up by the procedure employed in the two immediately preceding experiments. The only material isolated was 14.7 g. (88% recovery) of carbazole (mixed m.p.), melting at 239-242°.

Preparation of some heterocyclic sulfides

A series of sulfides has been prepared which might well be considered either under the Dibenzothiophene Derivatives heading or under this, the Nitrogen Heterocyclic Derivatives, heading. Since dibenzothiophene is a closed model of

diphenyl sulfide, aryl and heterocyclic sulfides might be considered open models of dibenzothiophene. All of the sulfides of the series contain at least one nitrogen heterocycle.

A brief report on these sulfides has been published;[311] the following is additional information to that found in this paper and variations from the general procedure reported therein will be given.

Preparation of 2-(benzylmercapto)-quinoline. In this experiment the sodium was added directly to a solution of the mercaptan in ethanol. The reaction mixture was refluxed for 18 hours. Thirty grams (0.24 mole) of benzyl mercaptan, 200 ml. of absolute ethanol, 4.7 g. of sodium and 33 g. (0.2 mole) of 2-chloroquinoline were employed. The yields were 74% (Run I) and 82% (Run II); m.p. 44-44.5°, b.p. 200-204°/2.5 mm. Recrystallization solvents employed were n-butanol and petroleum ether (b.p. 60-70°).

Anal. Calcd. for $C_{16}H_{13}NS$: S, 12.76. Found: S, 12.45, 12.47.

2-(Benzylmercapto)-quinoline hydrochloride was prepared by treatment of an ethereal solution of the quinoline compound with gaseous hydrogen chloride. The hydrochloride was

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311 H. Gilman, R. K. Ingham and T. C. Wu, J. Am. Chem. Soc., 74, 4452 (1952).

recrystallized from ethanol. The compound shrinks slightly on heating to 170° and decomposes at 187-190°. The yield was 86%.

Anal. Calcd. for $C_{16}H_{14}NSCl$: S, 11.16. Found: S, 11.34, 11.32.

The sulfone was prepared in the normal manner. The yield of 2-quinolyl benzyl sulfone was 54%, m.p. 187-190°.

Anal. Calcd. for $C_{16}H_{13}O_2NS$: S, 11.33. Found: S, 11.41, 11.52.

Preparation of 2-(n-dodecylmercapto)-quinoline. This reaction was run in the manner described for the octadecyl analog. The compound is a light yellow oil, b.p. 185-188°/2 mm.; the yield was 78%. In another run, using toluene as a solvent rather than ethanol, a 70% yield was obtained.

Anal. Calcd. for $C_{21}H_{31}NS$: S, 9.73. Found: S, 9.82, 9.84, 9.91. Calcd. $Mr_0^{25}$: 104.81. Found: 104.51.

Preparation of 2-(n-hexadecylmercapto)-quinoline. The procedure was the same as that for the octadecyl compound. The yield was 62%, m.p. 43-44°, b.p. 221-225°/0.5 mm.

Anal. Calcd. for $C_{25}H_{39}NS$: S, 8.31. Found: S, 8.50, 8.79, 8.54.

Preparation of 2-(n-octadecylmercapto)-quinoline. The complete procedure for this preparation has been reported.[311]

Anal. Calcd. for $C_{27}H_{43}NS$: S, 7.75. Found: S, 7.64, 7.59.

Preparation of 2-benzothiazolyl 2-quinolyl sulfide. The reaction mixture was refluxed for 24 hours. The product was not distilled but, following evaporation of the ethereal solution, the residue was recrystallized from dilute ethanol. The yield was 78% of light yellow crystals, melting at 109-111°.

Anal. Calcd. for $C_{16}H_{10}N_2S_2$: S, 21.78. Found: S, 21.69, 21.61

Preparation of 2-(4-phenylthiazolyl) 2-quinolyl sulfide. 2-Mercapto-4-phenylthiazole (Eastman Kodak, Yellow Label) and 2-chloroquinoline were the starting materials. The reaction mixture was refluxed for 24 hours. Recrystallization of the product from dilute ethanol followed by two recrystallizations from petroleum ether (b.p. 60-70°) gave 50% of yellow crystals, melting at 88-91°.

Anal. Calcd. for $C_{18}H_{12}N_2S_2$: S, 19.95. Found: S, 20.33, 19.72.

Preparation of 2-benzimidazolyl 2-quinolyl sulfide. The 2-thiolbenzimidazole (kindly provided by Parke Davis Company) was recrystallized from ethanol to give a m.p. of 311-312°. Two recrystallizations of the reaction product from petroleum ether (b.p. 77-115°) gave 60% of white crystals melting at 32.5-34°.

Anal. Calcd. for $C_{16}H_{11}N_3S$: S, 11.57. Found: S, 11.61, 11.70.

Preparation of 4-(7-chloroquinolyl) 2-benzothiazolyl sulfide. The reactants employed were 2-mercaptobenzothiazole (Eastman Kodak, Yellow Label) and 4,7-dichloroquinoline (kindly provided by National Aniline Corporation). Recrystallization of the crude product from ethanol, from glacial acetic acid, and from petroleum ether (b.p. 77-115°) failed to give a pure substance (m.p. 131-139°). The crude sulfide was dissolved in chloroform and extracted with 10% sodium hydroxide. The layers were separated and the solvent distilled from the chloroform solution. The product was recrystallized from petroleum ether (b.p. 77-115°) to give a 44% yield of 4-(7-chloroquinolyl) 2-benzothiazolyl sulfide, melting at 138-140°.

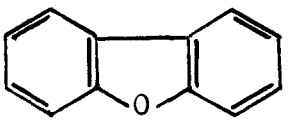
Anal. Calcd. for $C_{16}H_9N_2S_2Cl$: S, 19.49. Found: 19.35, 19.07, 19.39.

# DISCUSSION

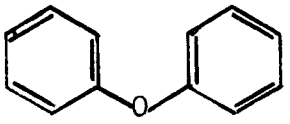
## Dibenzofuran Derivatives

Much of the experimental work of the investigations herein described has been directed toward the preparation of heterocyclic derivatives as possible antituberculous agents. The announcement by Barry[37] of the high antituberculous activity of 2-chloro-7-aminodibenzofuran was of considerable interest and further emphasized the need for additional research upon dibenzofuran derivatives.

Fortunately, the choice of which derivatives should be first considered was not a completely empirical one. Some investigations had been made with diphenyl ether derivatives.



Dibenzofuran



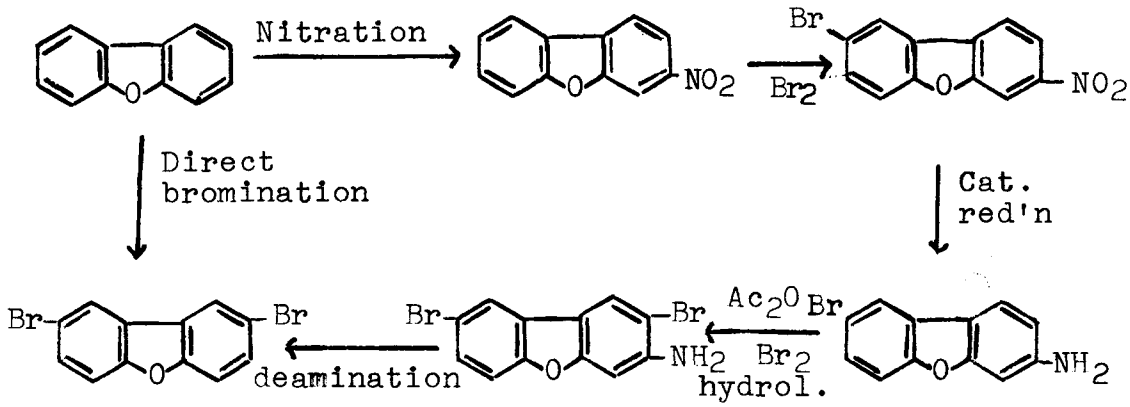
Diphenyl ether

Dibenzofuran may be regarded as a "closed model" of diphenyl ether. Thus, the information available from the diphenyl ethers was closely studied.

One of the more active diphenyl ethers is 2-chloro-4'-aminodiphenyl ether.[37] It has been shown that for high activity the chlorine atom must be either ortho or para to

the ether linkage and that additional chloro substitution in either ring leads to a marked increase in activity. Also, in research concerning substituted para-alkoxyphenylamines, it has been reported that substitution of a bromine atom for a chlorine atom does not decrease the activity, though the toxicity may be slightly increased. These findings indicated that the testing of an aminodihalodibenzofuran would be desirable. This led to the preparation and subsequent bromination of 2-bromo-3-acetaminodibenzofuran; bromine was chosen rather than chlorine since it is more convenient to work with and usually gives better yields. The purification of this bromination product proved rather difficult, and the isolation of products with different melting points indicated the formation of isomers. Analysis of the principal product indicated an acetamino-dibromodibenzofuran. This product was at first thought to be 2,8-dibromo-3-acetamino-dibenzofuran.

In an attempt to verify the structure of the above compound, 2-bromo-7-acetaminodibenzofuran was prepared and subsequently brominated. The product thus obtained was not identical with that obtained by bromination of the 2-bromo-3-acetamino analog. The bromination product from the 2-bromo-7-acetamino derivative was hydrolyzed to the amine and deaminated to give 2,8-dibromodibenzofuran.




Thus, the compound was established as 2,8-dibromodibenzofuran. The bromination product of the 2-bromo-3-acetaminodibenzofuran is probably 2,4-dibromo-3-acetaminodibenzofuran.

A more direct route to the 2,8-dibromo-3-aminodibenzofuran would be the nitration of 2,8-dibromodibenzofuran and the subsequent reduction of the nitro group. A report of this nitration reaction has been made by Yamashiro.[242] However, all attempts to duplicate his results have failed; some reaction definitely occurs but attempts to purify the resulting crude product by Yamashiro's procedure or by other methods were not successful. D. L. Esmay[14] studied the nitration of 2,8-dibromodibenzothiophene and reported considerable difficulty in purifying the product, the only material obtained in pure form being tentatively identified

as the 2,8-dibromo-3,7-dinitrodibenzothiophene-5-oxide.

It has also been reported that replacement of the amino group with an hydroxyl group in the diphenyl ether series results in little loss of activity and may lead to an increased potency.[37] Indeed, 4-hydroxy-4'-chlorodiphenyl ether is almost twice as active as 4-amino-4'-chlorodiphenyl ether.[37] Thus it was felt that the preparation of a 2-halo-8(or 7)-hydroxydibenzofuran would be informative. This led to an investigation of procedures for the preparation of hydroxydibenzofurans.

Hydroxy substituted dibenzofurans have been prepared from the corresponding bromo derivatives by the oxidation of Grignard compounds[312] and by alkali fusion in the presence of a catalyst in an autoclave.[156,313] The first method gives low yields and the second procedure, although it gives improved yields, is inconvenient. An experiment was conducted to determine if high temperatures and a catalyst were sufficient to bring about this reaction through the use of a high boiling solvent such as triethylene glycol, thus obviating the necessity for a bomb. A related procedure was carried out by Thirtle[314] in a reaction between

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[312] H. Gilman, W. G. Bywater and P. T. Parker, ibid., 57, 885 (1935).

[313] German Patent 606,350 [C. A., 29, 1434 (1935)].

[314] J. R. Thirtle, J. Am. Chem. Soc., 68, 342 (1946).

2-bromopyridine and potassium hydrosulfide. With bromodibenzofurans it was found, however, that the bromine atom was replaced by a hydrogen atom rather than by an hydroxyl group. The reductive debromination was found to take place with 2-bromodibenzofuran, 2,8-dibromodibenzofuran and 2,8-dibromodibenzothiophene. A brief report of these experiments has been published.[277] The experimental details for the reaction of the dibromodibenzothiophene as well as a review of debromination procedures can be found in the Doctoral Dissertation of D. L. Esmay.[14]

The isolation of 2-bromodibenzofuran when diethylene glycol was used as the reaction medium for 2,8-dibromodibenzofuran indicates that the reaction proceeds stepwise. The temperature factor seems to be quite important, a 50-55% yield of reduced product being obtained with triethylene glycol; a 32% yield being obtained with the lower boiling diethylene glycol, and no debromination product being isolated with ethanol as a solvent. A patent report of the use of kerosine as a solvent for the preparation of an hydroxyl derivative[315] led to an experiment using this solvent; only starting material was isolated.

It has been shown by Nef[316] and by Fry and

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[315] British Patent 181,673 [C. A., 16, 3762 (1922)].

[316] J. U. Nef, Ann., 335, 310 (1904).

co-workers[317] that alcohols and glycols react with alkali at elevated temperatures to yield hydrogen. While an explanation of the reductive debromination achieved in these cases might be based on the direct action of hydrogen produced, a more likely mechanism (reactions 1-4) would appear to be one similar to those recently proposed for the Meerwein-Pondorf-Verley reduction[318,319,320] and the reduction of ketones by primary alcohols.[321] Reactions 2 and 3 represent parts of a concerted process which occurs without the liberation of hydride ions as such. It is possible that an unidentified tarry residue, which was obtained whenever reductive debromination occurred, was formed by resinification of the aldehyde produced in accordance with reaction 4.

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317 (a) H. S. Fry, E. L. Schutze and H. Weitkamp, J. Am. Chem. Soc., 46, 2268 (1924); (b) H. S. Fry and E. L. Schutze, Ibid., 50, 1131 (1928).

318 L. M. Jackman and J. A. Mills, Nature, 164, 789 (1949).

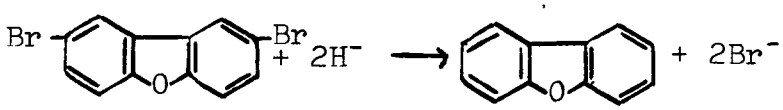
319 R. E. Lutz and J. S. Gillespie, J. Am. Chem. Soc., 72, 244 (1950).

320 W. E. Doering and R. W. Young, ibid., 72, 631 (1950).

321 G. H. Hargreaves and L. N. Owen, J. Chem. Soc., 750 (1947).

$$HOCH_2(CH_2OCH_2)_2CH_2OH + 2NaOH \longrightarrow NaOCH_2(CH_2OCH_2)_2CH_2ONa + 2H_2O \quad (1)$$

$$NaOCH_2(CH_2OCH_2)_2CH_2ONa \longrightarrow Na\overset{+}{O}CH(CH_2OCH_2)_2\overset{+}{C}HONa + 2H^- \quad (2)$$

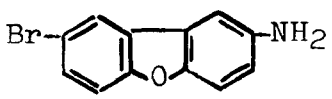



(3)

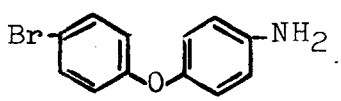
$$2Br^- + Na\overset{+}{O}CH(CH_2OCH_2)_2\overset{+}{C}HONa \longrightarrow 2NaBr + CHO(CH_2OCH_2)_2CHO \quad (4)$$

The ease with which the bromine atoms were replaced by hydrogen atoms suggests that the procedure described may be of use for the replacement of halogen by hydrogen in aromatic compounds and may also be of interest for proof of structure.

Since the 2-halo-4'-aminodiphenyl ethers have been shown to be of much greater activity than their 2'- and 3'-amino analogs, it was felt that 2-bromo-8-aminodibenzofuran should be prepared.

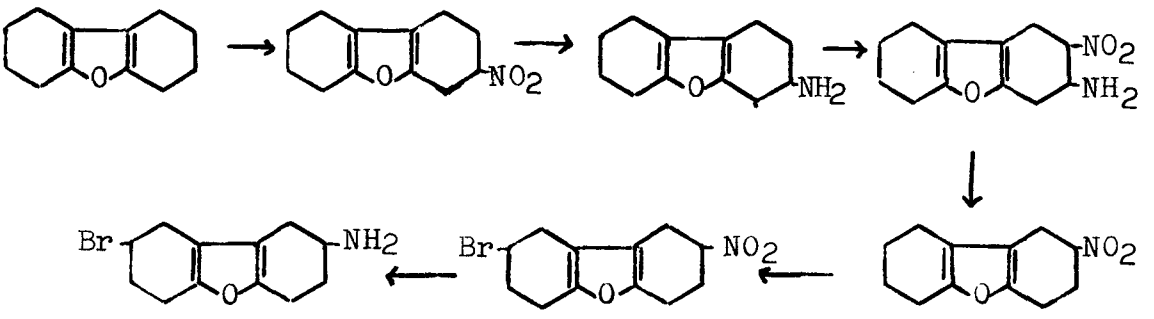



2-Bromo-8-amino-dibenzofuran




4-Bromo-4'-amino-diphenyl ether

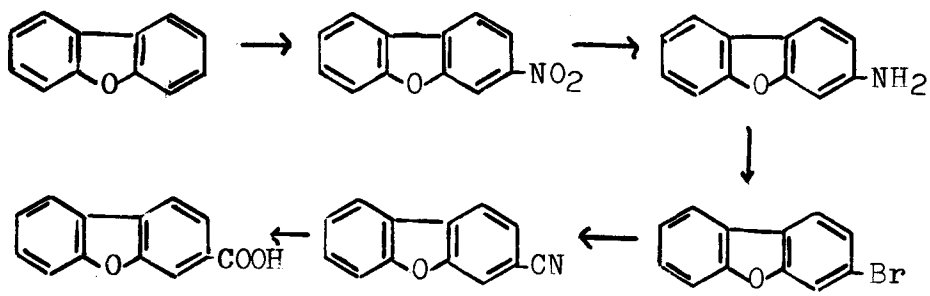
The sequence of reactions for the preparation of this compound was



This series of reactions was carried through up to the 2-bromo-8-nitro compound; however, at this point the quantity of compound was so small as to necessitate repetition of the entire sequence. If the reports from tests of the dibenzofuran compounds show any promise, the series certainly should be completed and the 2-bromo-8-amino compound tested. The 2-nitrodibenzothiophene is more accessible; thus the 2-bromo-8-aminodibenzothiophene has been prepared in the course of this investigation.

In addition to the replacement by an hydroxyl group, it was reported by Barry[37] that the replacement of the amino group of 4-chloro-4'-aminodiphenyl ether by a carboxyl group resulted in only slightly diminished activity. Application of this imformation to dibenzofuran made evident the desirability of testing the 2-halo-7-dibenzofurancarboxylic

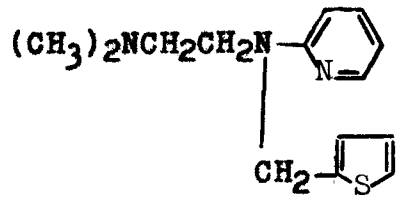
acid. Bromination of the 3-dibenzofurancarboxylic acid offered a means of preparing this compound; thus the preparation of the 3-acid was undertaken. The sequence for this preparation was



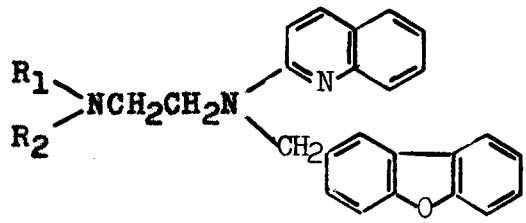

The 3-dibenzofurancarboxylic acid was prepared in this manner; however, the 3-cyanodibenzofuran was obtained in low yields and was found quite difficult to purify. Borsche and Bothe[134] prepared the 3-cyano derivative from the 3-bromo compound; however, purification by their procedure was not achieved. It was found more practical to hydrolyze the crude nitrile and to effect purification with the resulting acid.

In addition to the preparation of compounds as possible antituberculous agents, some studies were made of heterocyclic compounds which might possess high antihistaminic activity. Many compounds exhibiting favorable antihistaminic activity are dialkylaminoalkylamino derivatives containing

one aromatic (or heterocyclic) grouping linked directly to the nitrogen and another aromatic (or heterocyclic) grouping linked to the nitrogen <u>via</u> a methylene bridge (see Historical Section); for example, Histadyl has the structure



It was felt that dibenzofuran derivatives of the type



would possibly possess high activity and low toxicity.

This led to attempts to prepare 2-chloromethyldibenzofuran. The procedure given by Kirkpatrick[110] and several variations of this procedure were run in attempts to prepare the 2-chloromethyl compound; however, in each case upon heating under reduced pressure a green polymer was formed with the evolution of hydrogen chloride. Similar difficulties with the attempted preparation of 2-chloromethyldibenzofuran have been encountered by R. G. Johnson[322] and

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[322] R. G. Johnson, unpublished studies.

with the attempted preparation of 2-chloromethyldibenzothiophene by G. R. Wilder.[323] A recent note[324] concerning 2-chloromethylthiophene advocates stabilization of this compound with amines followed by rapid distillation under reduced pressure; this may well solve the problem of distillation of the 2-chloromethyldibenzofuran.

Interest in the amino-halodibenzofurans led to the consideration of the preparation of 2-bromo-6-aminodibenzofuran. A possible route to this compound would be the bromination of 4-nitrodibenzofuran with subsequent reduction of the nitro group. The only literature reference to the 4-nitrodibenzofuran was that of Yamashiro,[218] who reports its isolation along with the 1-, 2- and 3-nitro isomers as the result of the direct nitration of dibenzofuran. Though a number of workers have studied the nitration of dibenzofuran, Yamashiro is the only one to report the isolation of any save the 3-nitro compound.

A different route to the 4-nitrodibenzofuran was sought. 4-Aminodibenzofuran may be obtained by metalation of dibenzofuran with n-butyllithium, treatment of the 4-dibenzofuryllithium with O-methylhydroxylamine and subsequent hydrolysis. Many cases of replacement of the diazonium

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[323] G. R. Wilder, unpublished studies.

[324] Chem. Eng. News, 30, 3352 (1952).

group by the nitro group have appeared in the literature; a general review of the reaction through 1935 is available.[325] All of the earlier methods were of limited application. A report of a procedure of general application employing the diazonium cobaltinitrites has been published by Hodgson and Marsden.[286]

Since the 3-aminodibenzofuran is more accessible than the 4-isomer, the cobaltinitrite procedure was first run with the 3-amino compound. A 31% yield of pure 3-nitrodibenzofuran was obtained. Application of this procedure to the 4-amino derivative gave a 28% yield of 4-nitrodibenzofuran melting at 138-139°, the same m.p. reported by Yamashiro.

The method seems to be generally applicable for the preparation of nitrodibenzofurans and may be found beneficial in the preparation of difficultly accessible nitro compounds of similar systems, for example the 4-nitrodibenzothiophene.

## Dibenzothiophene Derivatives

Dibenzothiophene derivatives, especially substituted

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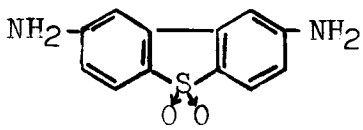
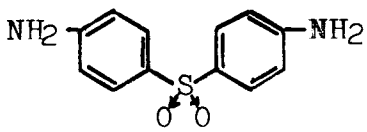
[325] K. H. Saunders, "The Aromatic Diazo Compounds and Their Technical Applications," E. Arnold and Company, London, 1936, p. 158.

5-dioxides, are closely related to substituted diphenyl sulfones; several of the most promising of antituberculous compounds are diphenyl sulfone derivatives (see Historical Section).

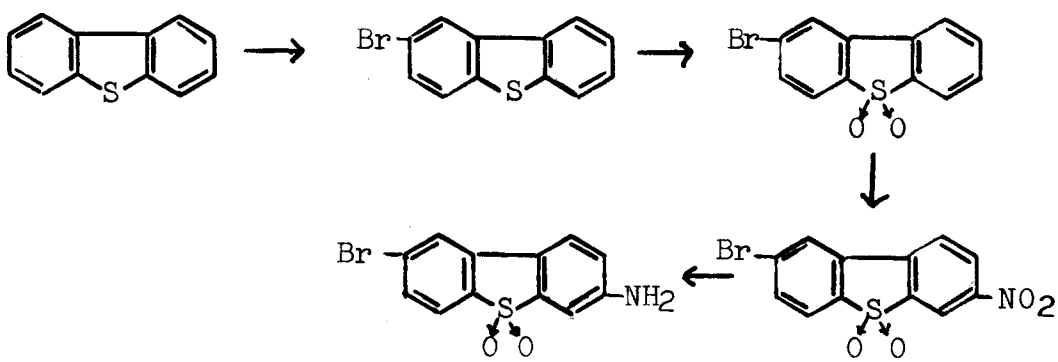


2,8-Diaminodibenzothiophene-5-dioxide



4,4'-Diaminodiphenyl sulfone

In view of this relation and the demonstrated activity of 2-halo-7-aminodibenzofuran, the preparation of 2-bromo-7-aminodibenzothiophene-5-dioxide was undertaken.

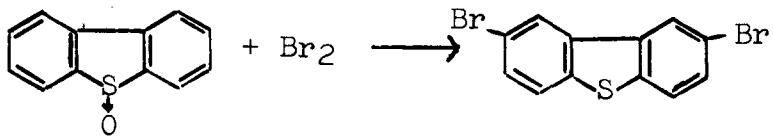


The compound was successfully prepared by the sequence of reactions shown above and is now being tested.

As was pointed out in the previous section of Dibenzofuran Derivatives, the 2-halo-8-amino derivative is actually

the closed model of the p-halophenyl p'-aminophenyl ethers and sulfones. The 2-nitrodibenzothiophene, contrary to the dibenzofuran analog, is accessible by direct nitration. The 2-bromo-8-aminodibenzothiophene was prepared by bromination of the 2-nitro compound and subsequent reduction of the nitro group. The 2-bromo-8-nitro- and 2-bromo-8-amino-dibenzothiophenes have been reported by Courtot,[287] but no experimental details were included in this report.

The nitration of dibenzothiophene-5-oxide has been shown to yield the 3-monosubstituted derivative.[298] It was thought that the reaction of the -5-oxide with bromine might give 3-bromodibenzothiophene-5-oxide; however, the product of this reaction has been identified as 2,8-dibromodibenzo-thiophene.




(1)

With hydrogen bromide, certain sulfoxides give halogen-addition products.[326]

$$R_2S\rightarrow O + 2HBr \longrightarrow R_2S\cdot Br_2 + H_2O \qquad (2)$$

Aromatic sulfoxides when treated with dry hydrogen chloride

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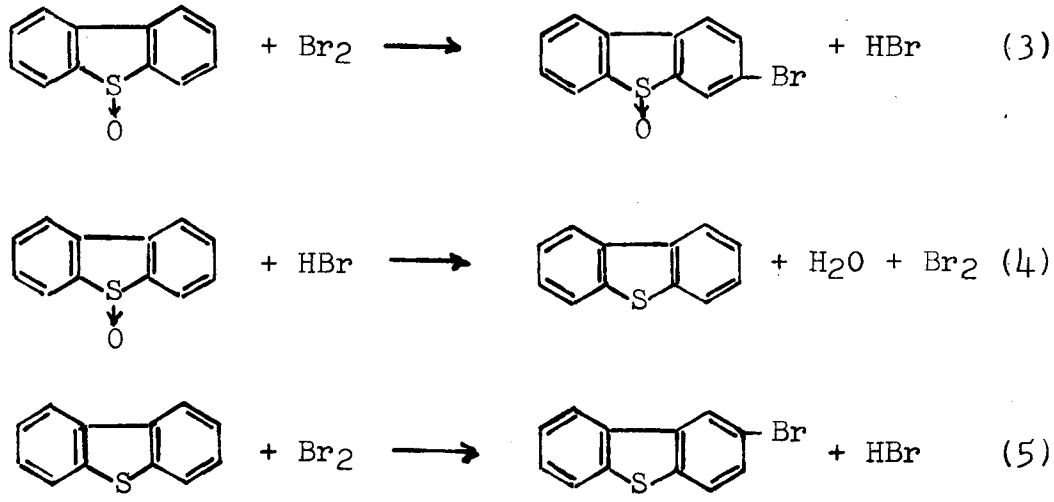
[326] H. Gilman, "Organic Chemistry," 2nd ed., Vol. I, John Wiley & Sons, Inc., New York, 1943, p. 872.

can be reduced to the corresponding sulfides;[327] this reaction may also give nuclear chlorination and even elimination of the sulfur atom.

The reaction of dibenzothiophene with chlorine gives first the -5-dichloride[298] and nuclear substitution if additional chlorine is employed. With bromine and dibenzothiophene, however, nuclear substitution proceeds, apparently without the formation of a stable -5-dibromide.[288] The analogous compound, dibenzoselenophene, forms the -5-dibromide,[328,329] which on heating above its melting point is converted to 2-bromodibenzoselenophene.

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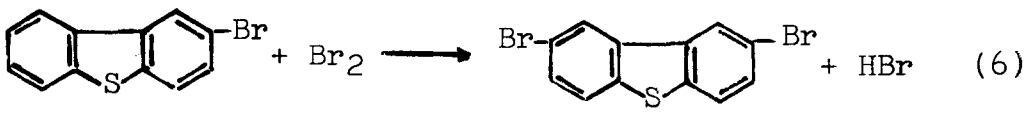
[327] M. Gazdar and S. Smiles, J. Chem. Soc., 97, 2250 (1910).

[328] C. Courtot and A. Matamedi, Compt. rend., 199, 531 (1934).

[329] O. Behagel and K. Hofmann, Ber., 72B, 697 (1939).



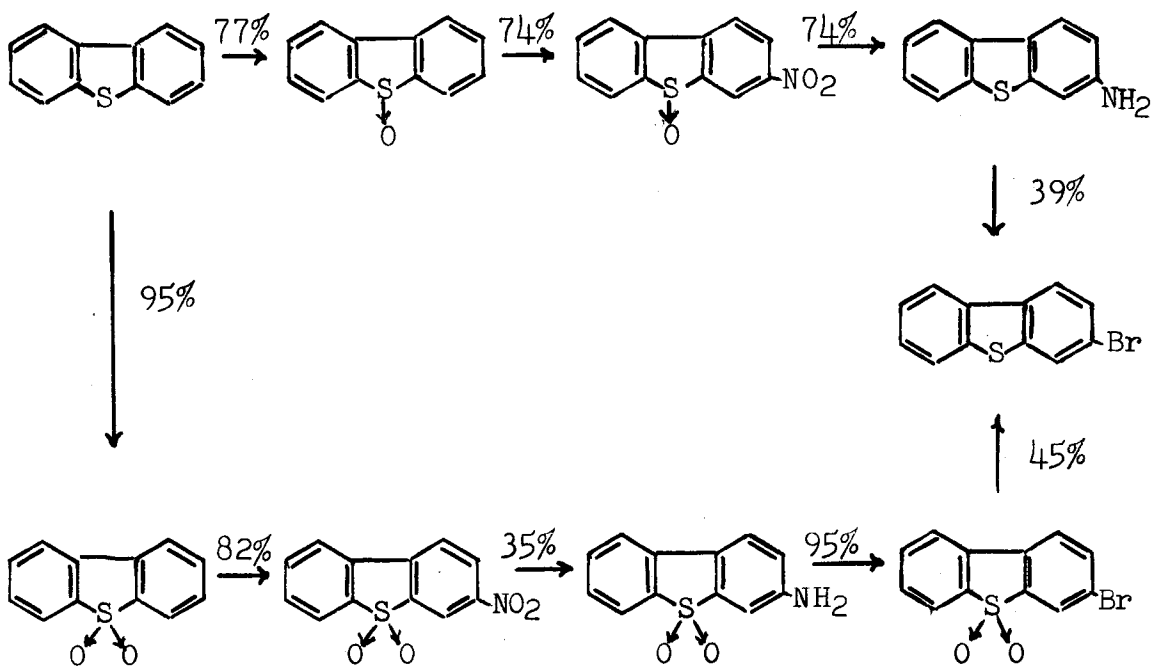

The probable mechanism of this reaction is illustrated by the above equations. The initial step may be a bromination of the -5-oxide (equation 3). The hydrogen bromide thus evolved could reduce some of the -5-oxide (equation 4); the dibenzothiophene would then be more readily brominated than the -5-oxide (equations 5 and 6) and this bromination would give additional hydrogen bromide for the reduction of the -5-oxide. The isolation of a small amount of dibenzothiophene supports this view.

Additional evidence in support of this sequence was obtained by reaction of the -5-oxide with bromine-free hydrogen bromide, a 33-44% yield of dibenzothiophene being obtained. The isolation of a trace of dibenzothiophene-5-dioxide was possibly due to the presence of this compound in the starting material.

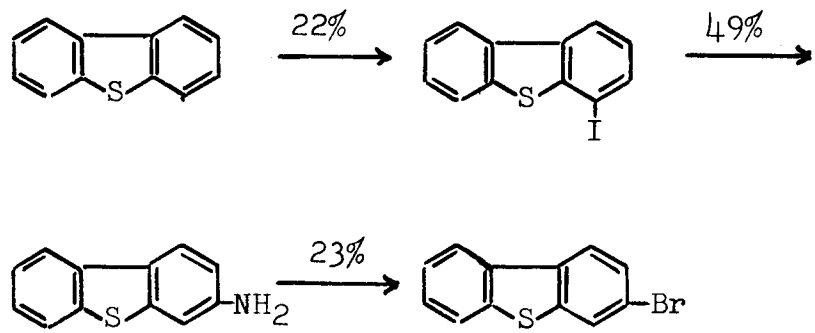
Buu-Hoi and Royer[120] have reported the bromination of dibenzothiophene with N-bromosuccinimide. An attempt to prepare the 3-bromodibenzothiophene-5-oxide by the use of this reagent employing the procedure of Buu-Hoi gave only starting material. Buu-Hoi and Royer also gave a procedure for the bromination of dibenzofuran with N-bromosuccinimide but did not state the yield; repetition of the procedure by

both this author and by R. G. Johnson[322] gave a very crude product which was difficult to purify.

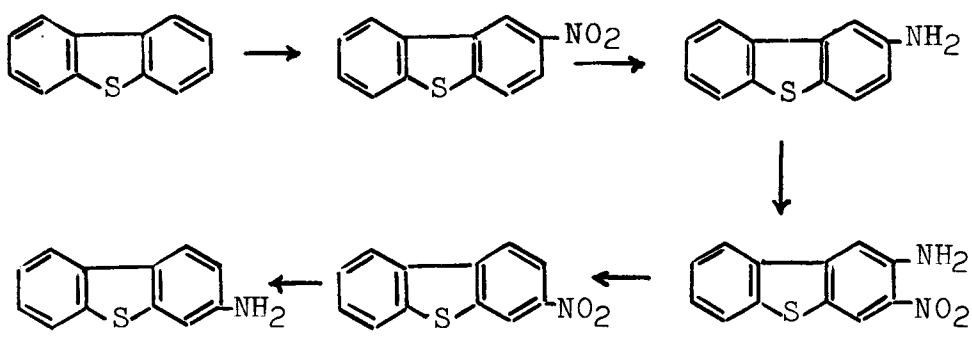
If the bromination of dibenzothiophene-5-oxide had resulted in the 3-bromo derivative, the latter compound could have been readily reduced, thus affording a useful route to the 3-bromodibenzothiophene. Since this route was not available, 3-bromodibenzothiophene was prepared by two more involved methods.



The yields are somewhat better with the -5-dioxide route; however, the monoxide synthesis involves one less step, the nitro grouping and the sulfoxide both being reduced in one step. Illuminati, Nobis and Gilman[301] prepared the 3-bromodibenzothiophene by a third method; however, the low yields make this sequence of reactions less desirable.




Another route to the 3-amino- and subsequently the 3-bromodibenzothiophene would be



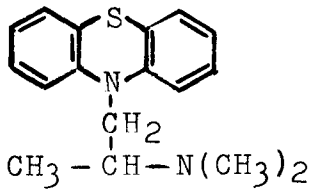
A review of the literature revealed the nitration by Gilman and Jacoby[294] of the 2-acetaminodibenzothiophene to give a mononitro derivative. Hydrolysis of this nitro-2-acetaminodibenzothiophene yielded an anomolous product containing no nitrogen. The unusual results of the report prompted a repetition of the reaction by this author; the results were essentially the same as those reported.

From the analysis reported by Jacoby for carbon, hydrogen and sulfur and assuming the remaining percentage to be oxygen (halogen tests were negative), the simplest formula is $C_8H_5OS$ (with a molecular weight of 149). A Rast determination indicated the molecular weight to be 163; thus, the compound is probably a monomer. A literature search for compounds of the above empirical formula revealed none melting near 88°. The compound shows neither acidic nor basic properties, thus eliminating groupings which would contribute these properties.

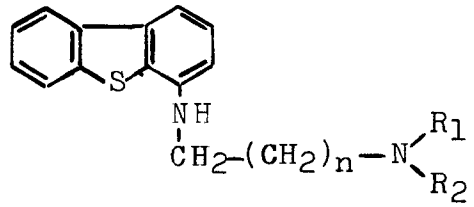
Bromination of 2-acetaminodibenzothiophene gives the 2-acetamino-3-bromo derivative.[306] By analogy, the nitro-2-acetaminodibenzothiophene was at first thought to be the 3-nitro compound. Infrared absorption measurements, however, indicate that the acetamino and nitro groups are not in the same ring. This finding makes it even more difficult to understand how normal hydrolysis of the compound gives a product containing no nitrogen.

J. F. Nobis[330] has reported obtaining a compound melting at 160-162° by hydrolysis with 50% hydrochloric acid of the nitro-2-acetaminodibenzothiophene; an analysis of this product was not included in the report.

One of the most effective of recent antihistaminic drugs is Phenergan (see Historical Section).



Phenergan



4-(Dialkylaminoalkylamino)-dibenzothiophene

It will be noted that the dialkylaminoalkylamino grouping in Phenergan is ortho to the sulfide linkage; this aroused interest in the preparation and testing of 4-(dialkylaminoalkylamino)-dibenzothiophenes, since in this case the group is also ortho to the sulfide bridge.

A number of 10-(dialkylaminoalkyl)-phenothiazines were first prepared by Gilman and Shirley;[89] however, they were tested only for antimalarial activity. A series of diethylaminopropylaminodibenzothiophenes, including the 4-derivative, was prepared by Gilman and Avakian;[306] these also were tested for antimalarial activity.

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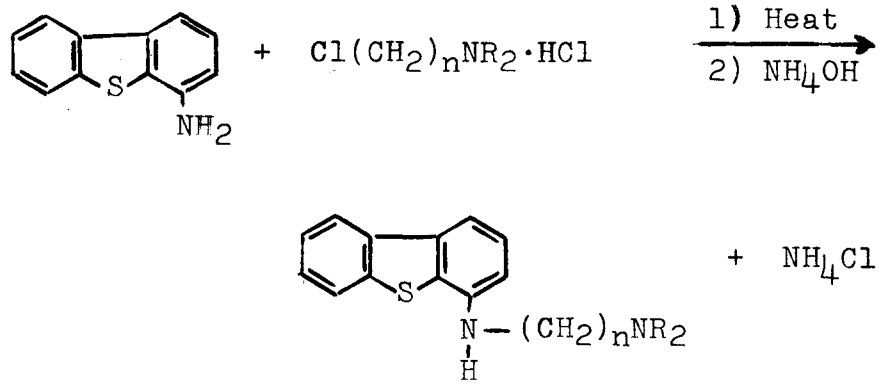
330 J. F. Nobis, private communication (1950).

4-Aminodibenzothiophene has been prepared by the Bucherer reaction (25% yield) and by amination of 4-bromodibenzothiophene (35% yield).[294] This compound is more conveniently prepared by reacting 4-dibenzothienyllithium with O-methylhydroxylamine.[306]

The method of alkylation of 4-aminodibenzothiophene was that of Gilman and Avakian.[98]




Due to the greater accessibility of the dimethylaminoethyl chloride hydrochloride, this reagent was reacted with the 4-aminodibenzothiophene in the initial run. Following the success of this reaction, the 4-(β-dimethylaminoisopropylamino)-dibenzothiophene was prepared.

## Nitrogen Heterocyclic Derivatives

In connection with some studies on the pharmacological activity of certain sulfur-containing compounds, a series of heterocyclic sulfides has been prepared.[311] Since dibenzothiophene is a closed model of diphenyl sulfide and

as all of the sulfides prepared incorporate at least one nitrogen heterocycle, the compounds offer a bridge between this and the previous (Dibenzothiophene Derivatives) section.

The germicidal properties of some sulfides[331] have been demonstrated. The antistreptococcal activity of 4,4'-diaminodiphenyl sulfone,[332] and the antituberculous effect of this and similar compounds,[50,333,334] and the indicated antimalarial activity[335] of its derivatives suggested the preparation of some quinolyl or other heterocyclic sulfides and sulfones.

Of interest was the effect of incorporating a fat-soluble group into the molecule with a view toward increased absorption of the drug by the animal body.[336]

The sulfides were prepared by treatment of the sodium mercaptide with the proper organic halide. The sodium

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331 N. E. Foss, F. Dunning and G. L. Jenkins, J. Am. Chem. Soc., 56, 1978 (1934).

332 G. A. H. Buttle, D. Stephenson, S. Smith, T. Dewing and G. E. Foster, Lancet, 1, 1331 (1937).

333 N. Rist, F. Block and V. Hamon, Ann. Inst. Pasteur, 64, 203 (1940).

334 G. W. Raiziss, Science, 98, 350 (1943).

335 H. Heymann and L. F. Fieser, J. Am. Chem. Soc., 67, 1979 (1945).

336 H. Gilman and S. P. Massie, ibid., 71, 744 (1949).

mercaptide was best prepared by addition of the mercaptan to a sodium ethoxide-ethanolic solution. In the preparation of the heterocyclic alkyl sulfides, the heterocyclic chlorides were employed; with the dodecyl sulfides, the dodecyl group was introduced *via* the mercaptan.

Of interest is the observation that quinine is oxidized in animals to 2-hydroxyquinine; thus the 2-substituted quinoline nucleus might be rendered more stable in the animal body.[337,338]

A report[339] that dibenzothiophene on treatment with a large quantity of Raney nickel in ethanol gave a 97.5% yield of diphenyl and a report[132] that dibenzofuran when treated with lithium in either dioxane or ether gave good yields of *o*-hydroxydiphenyl have stimulated interest in these reactions as methods for structure proof of certain heterocyclic derivatives. A review of the literature of reductive desulfurization and of cleavage reactions employing lithium has been compiled by D. L. Esmay.[14] Esmay repeated the cleavage of dibenzofuran with lithium in dioxane and obtained a 77%-80% yield of *o*-hydroxydiphenyl. With dibenzothiophene

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337 F. E. Kelsey, E. M. K. Geilung, F. K. Oldham and E. H. Dearborn, *J. Pharmacol.*, *80*, 391 (1944).

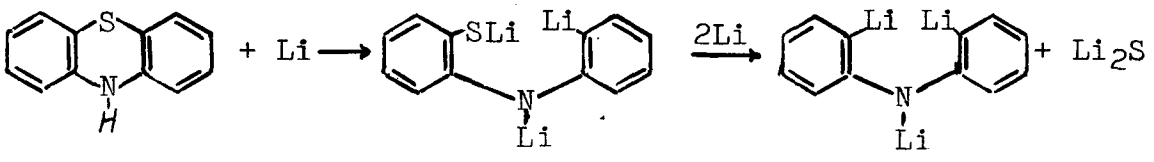
338 J. F. Mead and J. B. Koepfli, *J. Biol. Chem.*, *154*, 507 (1944).

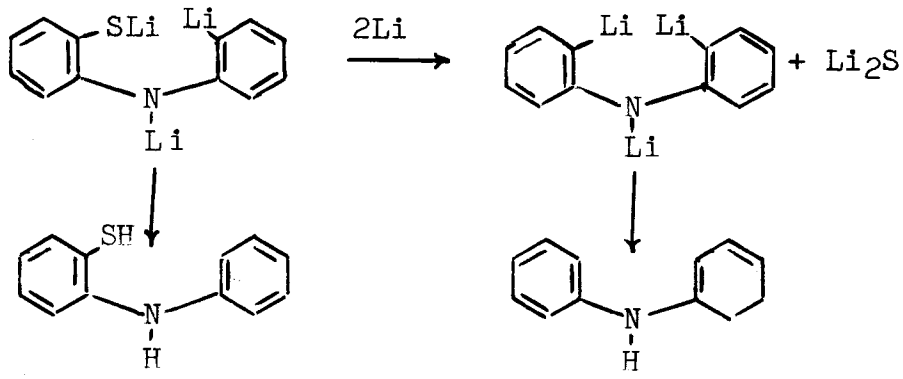
339 F. F. Blicke and D. G. Sheets, *J. Am. Chem. Soc.*, *71*, 4010 (1949).

there was obtained a 30.5% yield of diphenyl (without a nitrogen atmosphere) or a 16% yield of o-mercaptodiphenyl (with a nitrogen atmosphere).

It was thought desirable to extend the reaction to other heterocycles in order to determine its generality. With phenothiazine a 29% yield of o-mercaptodiphenylamine and a 4.4% yield of diphenylamine were obtained. Since some lithium remained after refluxing for 15 hours, it was assumed that the carbon-nitrogen bond is not cleaved under these conditions. To check this assumption, carbazole was reacted under similar conditions; an 88% recovery of starting material was obtained. To determine the effect of the imino hydrogen of phenothiazine and in order to investigate the reaction with substituted derivatives, the reaction was repeated using 10-ethylphenothiazine; a 24% yield of o-mercaptodiphenylethylamine was obtained.

The isolation of both o-mercaptodiphenylamine and diphenylamine from the reaction with phenothiazine may be explained by the mechanism proposed by Esmay[14] for the cleavage of dibenzothiophene as shown:






The failure to obtain a positive Color Test I[285] and to isolate any carboxylic acid on carbonation was also considered by Esmay. It was concluded that the cleavage of phenothiazine (and 10-ethylphenothiazine) by lithium in refluxing dioxane probably yields an intermediate compound containing a carbon-metal linkage which is immediately destroyed through reaction with the dioxane.

## Suggestions for Further Research

A critical survey of the known derivatives of dibenzofuran and dibenzothiophene reveals many widely varying physical constants reported for identical compounds. A clarification of these inconsistencies would be a considerable aid to investigators in these fields.

If the physiological tests of the bromo-amino derivatives of dibenzofuran and dibenzothiophene indicate appreciable activity, other compounds should be prepared to study

the effect of position and of additional substitution. The 1-amino-8-bromo- and 2-bromo-6-aminodibenzofurans would be of particular interest. Also of interest would be a study of the effect of replacement of the amino by other groupings, such as a carboxyl or hydroxyl group.

The possible extension of reductive debromination should be studied. The ease with which debromination takes place in high-boiling solvents suggests that the reaction might be of use for structure-proof purposes. With bromo derivatives of dibenzofuran containing other substituents, the effect of the reaction conditions upon these various substituents deserves consideration.

Also of interest in connection with structure-proof studies is the desulfurization of dibenzothiophene and phenothiazine derivatives with lithium in dioxane. This reaction has been studied only with dibenzothiophene, phenothiazine and 10-ethylphenothiazine; the reaction should be run with a series of substituted derivatives in order to determine its limitations.

The reductive bromination of dibenzothiophene-5-oxide by hydrogen bromide is of considerable interest and should be extended to substituted derivatives and to other heterocycles, such as phenothiazine-5-oxide.

The use of amines to stabilize chloromethyl compounds[324] should be applied to the preparation of

2-chloromethyldibenzofuran in an attempt to prevent polymerization.

The compound obtained upon nitration of 2-acetaminodibenzothiophene and the subsequent hydrolysis of this nitro-2-acetaminodibenzothiophene to yield a nitrogen-free substance deserves additional experimentation. The effect of a variation in conditions of hydrolysis and the identity of the anomalous product present an interesting problem for study.

## SUMMARY

A survey of the chemotherapy of tuberculosis has been presented. A brief review of important physiologically active dialkylaminoalkylamines has also been included.

Supplementary listings of known derivatives of dibenzofuran and dibenzothiophene have been prepared.

A number of bromo-nitro and bromo-amino derivatives of dibenzofuran and dibenzothiophene have been prepared.

Alkali fusion of 2-bromo and 2,8-dibromodibenzofuran when carried out in high-boiling glycols gave reductive debromination.

The replacement of an amino by a nitro group was found to be reasonably applicable to dibenzofuran derivatives.

A series of attempts to prepare 2-chloromethyldibenzofuran, avoiding polymerization of the product, was made.

Dibenzothiophene-5-oxide was found to be reduced and subsequently brominated by treatment with either bromine or hydrogen bromide.

The reaction of lithium with phenothiazine, 10-ethylphenothiazine and carbazole in dioxane was investigated. Cleavage occurred only with the first two of these compounds.

A series of heterocyclic sulfides was prepared.