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Synthetic antimalarials of polynuclear heterocycles containing oxygen and sulfur

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NOTE TO USERS

SYNTHETIC ANTIMALARIALS OF POLYNUCLEAR HETEROCYCLES CONTAINING OXYGEN AND SULFUR

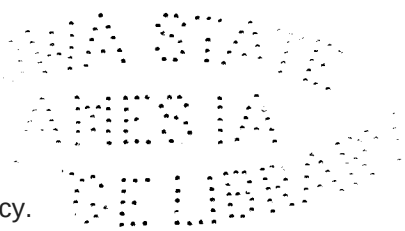
by

Souren Avakian

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry



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1944

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1126-98

TABLE OF CONTENTS

INTRODUCTION

Malaria results in greater morbidity and mortality than any other infectious disease. Although its incidence is world-wide, it is a most important tropical disease because it has hindered the industrial and agricultural development of the tropics. Up to a few years ago, one third of the working time in the southern United States was lost because of the Anopheline mosquito. At the present time, in tropical countries, the loss in time is often estimated to be as high as from 50 to 75 per cent. In the United States, it is roughly estimated that there are nearly 1,000,000 cases resulting in 5,000 deaths annually[1]. In India alone, an estimated 100,000,000 cases occur which result in nearly 1,000,000 deaths each year. Adequate statistics regarding the morbidity and mortality of malaria do not exist. The sum total of malaria at the present time cannot even be closely estimated. However, from such data as are available, it may be assumed that there are at least 300,000,000 cases of malarial fevers resulting in not less than 3,000,000 deaths each year throughout the world[2]. Although the disease has been known since earliest time by such names as chills and fever and Roman

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[1] Coggeshall, J. Am. Med. Assoc., 112, 8 (1943).

[2] Russell, Bull. N. Y. Acad. Med., 19, 599 (1943).

fever, it was not until 1880 that Laveran, a French military surgeon, discovered the cause of the disease. The incidence of the disease is highest in regions of swamps and marshes which are ideal breeding places for the Anopheline mosquito. It is this mosquito which serves to transmit the causative agent of the disease to human beings.

Quinine is the natural antimalarial. The two most important synthetics are atabrine and plasmoquin. Plasmoquin is the most toxic of the antimalarials commercially available. Neither quinine nor atabrine alone is as useful as a therapeutic agent as are both used together. While the atabrine supply is adequate for immediate needs, it will be necessary for its production to be increased to meet the requirements of our troops engaged in warfare in the tropics. The supply of quinine is very small. The present stocks of quinine were frozen some time ago[3], and their use restricted to the treatment of malaria.

The need for an efficient antimalarial among our armed forces in the tropics is heightened by the fact that they will be entirely lacking in immunity while in highly malarious areas. At one time or another they will all be exposed to malaria while physical and mental strain will have lowered their resistance. Unfortunately, many of them will also be wounded. Under these conditions, it is highly probable that latent cases of malaria will be incited.

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[3] War Production Board, Quinine Order M-131.

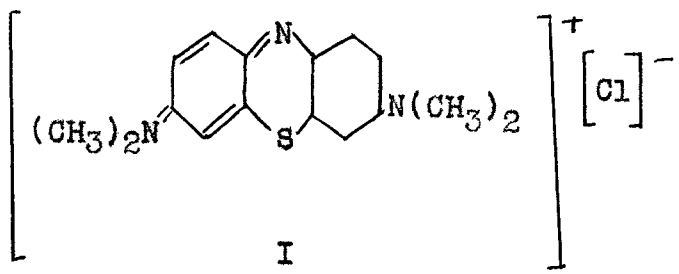
Because of the abnormal conditions encountered in the tropics, the present antimalarials are, for the most part, inadequate. Quinine, plasmoquin and atabrine are alike in that they are unable to cure without the occurrence of relapses in a certain percentage of cases. They also fail to prevent infection by sporozoites when administered in safe doses.[2] What is needed is a true causal prophylactic which would prevent infection with malaria. Such an antimalarial would speed the victory in the present war and would help in developing the tropics in the peace that follows. Also, it would be of tremendous value in helping to minimize the danger of the spread of the disease to the civilian population from returning service men infected with malaria.

HISTORICAL

It is necessary to review the cycle of malaria in order to understand and consider the chemical attack on the malarial parasite. The treatment of malaria is made difficult because of the specificity of drugs for the various forms of the parasite and by the complexity of the infection. There are at least three species of malarial parasites which commonly infect man. They are the causative agents of the three types of the disease which are known as tertian, quartan and quotidian malaria. The life cycle of all of the causative agents is essentially the same. The life cycle begins with the sporozoite stage. This is the form in which the disease is transmitted from the mosquito to man. In man, the parasite passes through the schizont stage and then to the gametocyte stage. It is in this last stage that the disease is transmitted from man back to the mosquito. Early workers have thought that the reactions of these several forms of malaria to various therapeutic agents differed greatly. This led to the conclusion that there was a great deal of specificity among drugs. However, this conclusion has tended to be minimized among present-day investigators, especially in regard to the specificity of a drug for the schizonts and gametocytes.

Plasmoquin

The extensive research by a group of workers of the I. G. Farbenindustrie resulted in the most important advances in the chemotherapy of malaria. Guttman and Ehrlich[4] had shown in 1891 that methylene blue (I) exhibited some antimalarial action. Consequently Schulemann[5] began his investigation by modifying the methylene blue molecule and found that the compound (II) possessed enhanced activity. The introduction of similar groups in the quinoline molecule eventually led to the development of Plasmoquin (III). Plasmoquin is one of the most potent antimalarials; it is about sixty times as effective as quinine in avian malaria.



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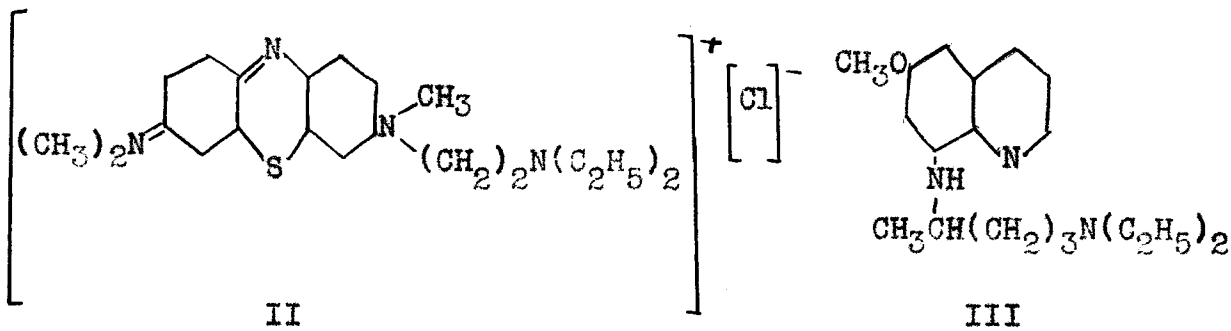


II III

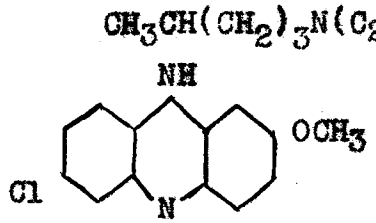
[4] Guttman and Ehrlich, Berlin. klin. Wochschr., 28, 593 (1891). Chem. Zentr., I, 291 (1892).

[5] Schulemann, Proc. Roy. Soc. Med., 25, 897 (1931-32).

Its effectiveness against gametocytes, especially those of P. falciparum, is unique. When administered in safe doses, it reduces the number of relapses, but unfortunately, does not eliminate them. Its administration is safe only under medical supervision. The most common toxic effects are cyanosis and methemoglobin formation[6].

Atabrine

The introduction of similar substituents in several other heterocyclic ring systems led Mietzch and Mauss[7] to the synthesis of atabrine (IV) which proved to be a schizonticidal drug. In avian malaria, it is fifteen times less effective than plasmoquin but four times more effective than quinine. The toxicity of atabrine is considerably lower than that of plasmoquin. Abdominal pain, and headache are occasionally noted. The skin turns yellow in about 50% of the patients, but this is harmless and the color usually disappears in about fifteen days after discontinuation of the treatments. Its advantage over quinine is that it does not cause cinchonism.



IV

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[6] Fischer and Rheindorf, Arch. Schiffs - Tropen -Hyg., 32, 594 (1928). [C. A., 23, 3020 (1929)].

[7] Mietzch and Mauss, Angew. Chem., 47, 633 (1934) [C. A., 28, 7360 (1934)].

Other Ring Systems

In addition to thousands of quinoline and acridine derivatives, a large variety of other ring systems have been examined as potential sources of antimalarials. In most cases, when the results have been negative, the compounds under question contained a few or no active substituents. Hence, further investigation is necessary to establish, with some degree of certainty, that a given ring system is unsuitable for antimalarial synthesis as has been done in the case of naphthalenes and the benzothiazoles. For example, the introduction of the active substituents of plasmoquin and atabrine into triphenylmethane and thiazine have produced active compounds[8]. Mottier[9] has demonstrated that 4-amino- and 4-γ-aminopropylaminocarbazoles were ineffective against the malarial organism, but this study does not establish the ineffectiveness of the carbazole ring as a base for antimalarial synthesis.

Dibenzofuran

The dibenzofuran molecule was first examined as a possible source of antimalarials by I. G. Farbenindustrie[10]. They

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[8] Mietzch and Mauss, Klin. Wochschr., 12, 1276 (1933) /C. A., 28, 827 (1934)/.

[9] Mottier, Helv. Chim. Acta., 17, 1130 (1934).

[10] I. G. Farbenindustrie A. -G.: British patent 373,624. Aug. 20, 1931 /Brit. Chem. Abstracts, B, 912 (1932)/.

prepared a series of eight compounds (Table I) without reporting the pharmacological assays.

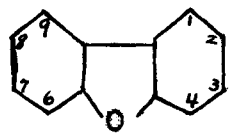
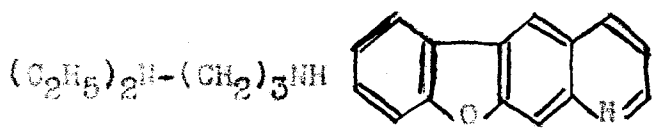


Table I

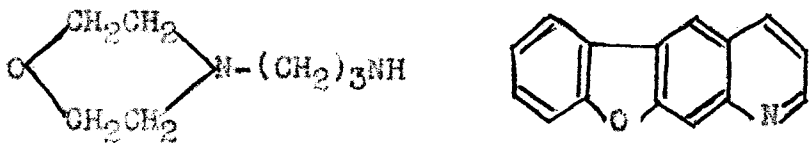
Substituent in Position 3	Other Groups	Activity
$-N(CH_2CH_2NEt_2)_2$		
$-N(CH_2CH_2NEt_2)_2$	7-$N(CH_2CH_2NEt_2)_2$	
$-NHCH_2CHOHCH_2NC_5H_{10}$		
$-NHCH_2CH_2OCH_2CH_2NEt_2$		
$-NHCH_2CH_2SCH_2CH_2NEt_2$		
	2-$N(CH_2CH_2NEt_2)_2$	
	2-$N(CH_2CH_2NC_5H_{10})_2$	
	2-$N(CH_2CH_2OCH_2CH_2NEt_2)_2$	

However, it is quite possible that their compounds were only slightly active at best, since the alkyl side-chains used by them are not very effective and the compounds do not contain additional functional groups such as methoxy, methyl, or chloro.

More recently Roger Adams and co-workers[11] synthesized aminobenzofuroquinolines which resemble plasmoquin in their basic structure. They nitrated benzofuro [3,2-g] quinoline, reduced it, and condensed the corresponding amine with 3-chloro-N,N-diethylpropylamine hydrochloride to give (3-diethylamino-propylamino)-benzofuro [3,2-g] quinoline (V), and with N-(3-chloropropyl)morpholine hydrochloride to give [3-(4-morpholinyl)-propylamino]-benzofuro [3,2-g] quinoline (VI).



V



VI

Starting with 2-nitro-3-aminodibenzofuran they prepared 5-aminobenzofuro [3,2-f] quinoline and condensed it with N-(3-chloropropyl)-morpholine hydrochloride. Neither the resulting 5-[3-(4-morpholinyl)-propylamino]-benzofuro [3,2-f] quinoline (VII) nor the compounds (V) and (VI) showed antimalarial activity.

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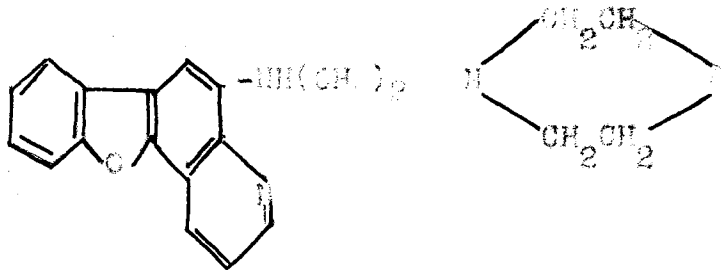
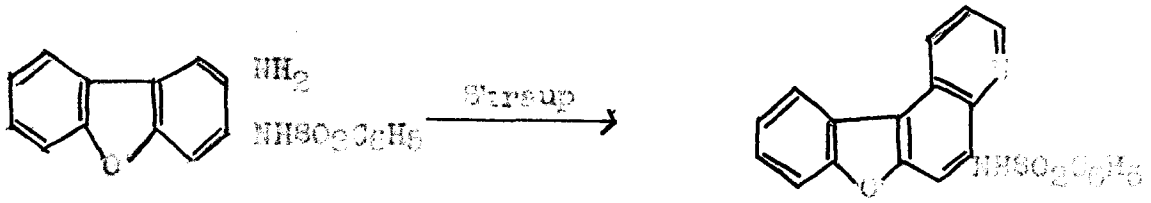
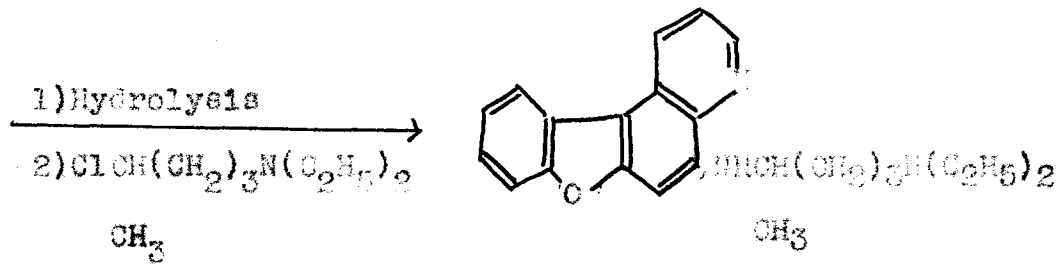
[11] Adams, Clark, Kornblum and Wolff, J. Am. Chem. Soc., 66, 22 (1944).



VII

8-[4-Diethylamino-1-methylbutylamino]benzofuro [3,2-e]-quinoline (VIII) which resembles much more closely the base from which the plasmoquin molecule is derived, was prepared through the following set of reactions:





VIII

The pharmacological results are not reported for this compound.

Obviously, the number of dibenzofuran derivatives tested for possible antimalarial activity is too few and information regarding their physiological activities too incomplete to supply any information as to the effectiveness of the dibenzofuran nucleus. However, a large number of dibenzofurnan derivatives has been prepared and tested for analgesic action. Of the one hundred and sixteen derivatives of dibenzofuran which have been submitted from this laboratory to be tested for analgesic action, nineteen (16%) have shown some analgesic activity. Only two of the compounds, 4-aminodibenzofuran and the more complex 2-methyldibenzofuro [2,3-d]-imidazole have manifested significant analgesic activity. These results are encouraging and definitely indicate that the dibenzofuran is a promising base for pharmacologically active compounds. It is believed that further study may prove many of these compounds to be active antimalarials as well as active analgesics.

Dibenzothiophene

No dibenzothiophene derivatives have been mentioned in literature as having been tested for possible antimalarial activity. This does not include any compounds that may be listed in confidential reports prepared under the auspices of the United States Government. In fact, only a very small number of dibenzothiophene derivatives have been prepared and submitted for physiological tests.

It is both surprising and disappointing to find that so little work has been done on dibenzothiophene since the possibility of oxidation of the nuclear sulfur of dibenzothiophene opens a wide field of investigation unattainable with the analogous dibenzofurans and carbazoles. Some of the sulfoxides and sulfones now being studied are found to possess strong antistreptococcic activity. A brief review of some of the latest discoveries in this field will make readily apparent the similarity between already known agents and the possible dibenzothiophene oxidation products.

At first it was considered that sulfanilamide was the most important agent in the cure of streptococcic infections and a theory was advanced that other active agents owe their antistreptococcic activity to the fact that they undergo conversion in the body to sulfanilamide[12]. Recent developments of more immediate interest cast doubt upon the validity of this theory as to the mode of action. Buttle and co-workers[13] have demonstrated the high degree of potency of 4,4'-dinitro- and 4,4'-diaminodiphenyl sulfone. The former was less toxic and equally as active in mice as sulfanilamide. The diamino-compound was found to be 100 times as active as sulfanilamide and 25 times as toxic, giving it an effectiveness of about four

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[12] Trefouel, Trefouel, Nitti, and Bovet, Presse. Med., 45, 839 (1937) [C. A., 31, 8695 (1937)].

[13] Buttle and co-workers, Lancet, 1937 (1), 1331 [C. A., 31, 7118 (1937)].

times that of the older agent. Andre and Guy[14] studied the corresponding sulfoxides and found the maximum activity in 4-nitro-4'-aminodiphenyl sulfoxide and the corresponding sulfone. In either case this activity was reported as being about 100 times that of sulfanilamide.

Coggeshall[15] found sulfanilamide therapy to be successful in monkeys infected with P. knowlesi. A residual immunity lasted for three months after eradication of the infection. Sulfapyridine, when administered in massive doses has a definite lethal action against P. knowlesi in rhesus monkeys[16]. Sulfathiazole was also found effective in simian malaria[17]. More recently, Coggeshall[18] and Marshall[19] have demonstrated the effectiveness of 4,4'-diaminodiphenyl sulfone and its derivatives as antimalarial agents. All the available data indicate that most of the compounds which are active against streptococcic infections are also active antimalarials.

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[14] Andre, Andre, and Guy, Nature, 140, 283 (1937); Lavadite, Andre, Vaisman, Andre, and Guy, Compt. rend. 205, 1018 (1937).

[15] Coggeshall, Am. J. Trop. Med., 18, 715 (1938).

[16] Singh and Singh, J. Malaria Inst. India, 2, 181 (1939) [C. A., 33, 1818 (1939)].

[17] Dikshit and Ganapathi, Ibid., 3, 525 (1940) [C. A., 34, 5567 (1940)].

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

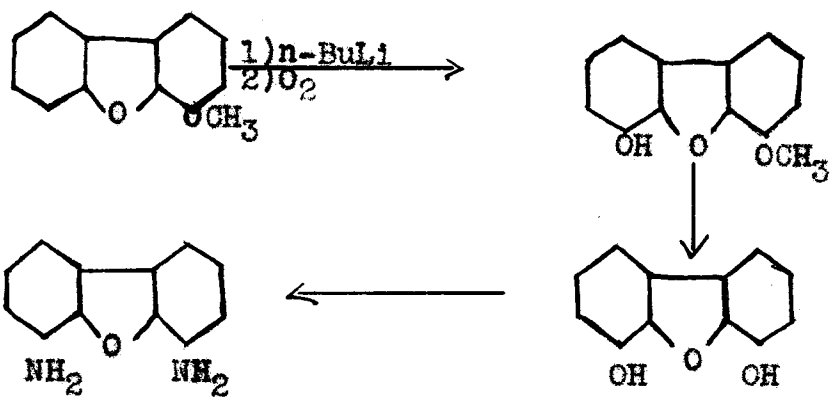
[19] Marshall, et al, J. Pharm. Exptl. Therap., 75, 89 (1942) [C. A., 36, 4196 (1942)].

DISCUSSION

Dibenzofuran

Amination of 4,6-diiododibenzofuran.

Cheney[20] has prepared 4,6-diaminodibenzofuran through the following set of reactions:

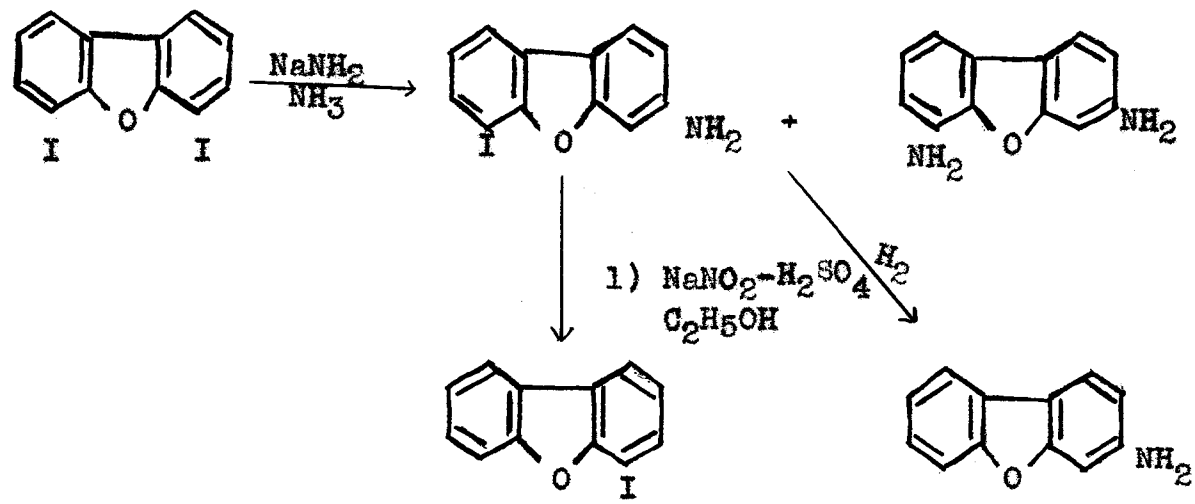


The amination of 4,6-diiododibenzofuran was undertaken with the hope of obtaining the above diamino compound more conveniently and economically. However, the compounds isolated from various attempts were 4-aminodibenzofuran, 3-aminodibenzofuran, 3-amino-6-iododibenzofuran, and a diaminodibenzofuran. These results were both disappointing and surprising

[20] Gilman and Cheney, J. Am. Chem. Soc., 61, 3149 (1939).

inasmuch as Bradley[21] had successfully prepared 2- and 4-aminodibenzofuran in good yields by reacting the corresponding bromides with sodamide. Swislowsky[22] has prepared 2,8-diaminodibenzofuran in somewhat lower yields through the same reaction. Aminodibenzofurans have also been prepared by high temperature and pressure amination of the corresponding bromides[22,23].

The 4,6-diiododibenzofuran reacts with sodamide in liquid ammonia to give 3-amino-6-iododibenzofuran and a small amount of diaminodibenzofuran, m.p., 154°. The structure of the 3-amino-6-iododibenzofuran was established in the following way. Catalytic deiodination gave 3-aminodibenzofuran and the replacement of the amino group with hydrogen, by way of diazotization, yielded 4-iododibenzofuran.



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[21] Bradley, Doctoral Dissertation, Iowa State College, (1937).

[22] Swislowsky, Doctoral Dissertation, Iowa State College, (1939).

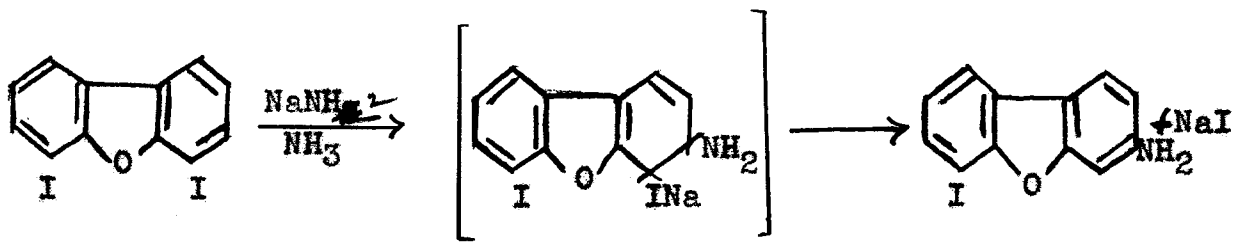
[23] Bywater, Doctoral Dissertation, Iowa State College, (1934).

Thus, the product must be 3-amino-6-iododibenzofuran. A 3-amino-4-iododibenzofuran would give the same product but the possibility of a hetero-rearrangement can be excluded. A large depression in melting point was observed when the diaminodibenzofuran was mixed with an authentic specimen of 4,6-diaminodibenzofuran (m.p., 152°). In all probability, this diaminodibenzofuran was formed from 3-amino-6-iododibenzofuran. Therefore, one of the amino groups must be in the 3-position and the other in either the 6, 7, 8, or 9-position. A mixed melting point with 2,7-diaminodibenzofuran (m.p., 152°) and 3,7-diaminodibenzofuran (m.p., 150-152°) eliminated positions 7 and 8. Since a rearrangement from the 6-position to the 9-position is rather improbable, the compound was assumed to be 3,6-diaminodibenzofuran.

When a mixture of anhydrous ethyl ether and liquid ammonia was used as solvent, only 3-aminodibenzofuran was isolated. The yield was 42%. Obviously one of the iodo groups was removed through reduction. Since the only difference between the two runs was the presence of ethyl ether in the latter, it may be possible that the ether dissolved the intermediate 3-amino-6-iododibenzofuran and facilitated the removal of the iodo group.

Similar rearrangements are not listed in the literature and it is impossible to present an adequate explanation for the mechanism of the reaction from the available data. The formation of a complex with one of the iodo groups, which in turn

might decompose in such a way as to give 3-amino-6-iododibenzofuran, is not likely. Competitive reactions indicate that sodamide reacts more readily with bromobenzene than with iodobenzene[24]. By analogy, the 4-bromodibenzofuran would form a complex with sodamide more readily than one of the iodo groups of 4,6-diiododibenzofuran and rearrange to give 3-aminodibenzofuran, yet the amination of 4-bromodibenzofuran proceeded normally to give 4-aminodibenzofuran. Another possibility is the addition of sodamide to the double bond, activated by the iodo group, followed by elimination of sodium iodide.



Again this is not likely since there is no evidence that sodamide adds even to the most active carbon-to-carbon double bonds. Perhaps further study of the reactions involved will reveal facts which will be helpful in determining the reason for the rearrangement.

High temperature and pressure amination yielded a small amount (11%) of 4-aminodibenzofuran. There was no evidence of

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[24] Bergstrom and Fernelius, Chem. Rev., 20, 413 (1937).

rearrangement in this reaction and it might be possible to obtain 4,6-diaminodibenzofuran by using milder conditions. The high temperature (180-185°) employed in this reaction might have brought about the removal of the iodo group through reduction.

It is of interest to note that catalyzed hydrolysis of 4,6-diiododibenzofuran proceeds normally. 4,6-Dihydroxydibenzofuran was obtained in 75% yield by heating the corresponding diiododibenzofuran with concentrated sodium hydroxide and copper sulfate at 220°.

Nitration.

Whereas the nitration of 2-hydroxydibenzofuran[25] yields an unidentified dinitro compound, the nitration of 2-methoxydibenzofuran with fuming nitric acid gives 2-methoxy-3-nitrodibenzofuran in 73% yield. The structure was established as follows:

The nitro compound was reduced to the corresponding amine and the amino group replaced with bromine. The bromo-methoxy compound was shown to be 2-methoxy-3-bromodibenzofuran by a mixed melting point. The structure of 2-methoxy-3-bromodibenzofuran had been previously established by Van Ess[26] who had

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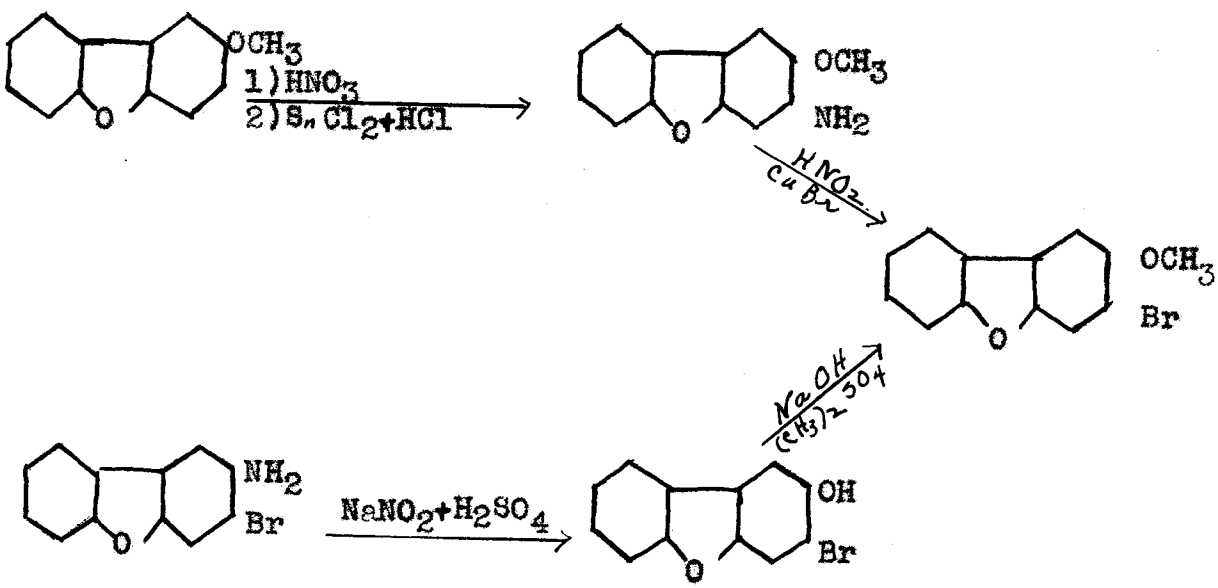
[25] Gilman, Jacoby, and Swislowsky, J. Am. Chem. Soc., 61, 954 (1939).

[26] Gilman and Van Ess, ibid., 61, 1365 (1939).

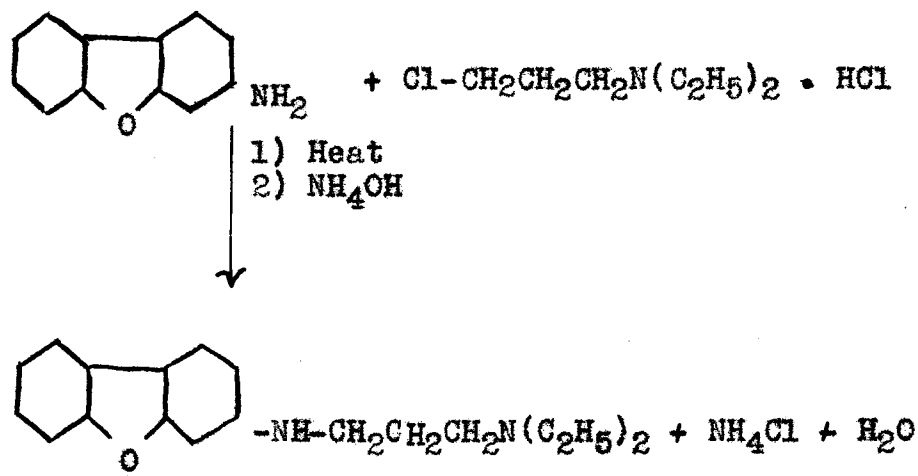
converted the amino group of 2-amino-3-bromodibenzofuran through diazotization, to the hydroxyl group, followed by methylation to a methoxyl group. He had also obtained the same compound by brominating 2-methoxydibenzofuran.



1-Nitro-3,4-dimethoxydibenzofuran was obtained in 96% yield by nitrating a solution of 3,4-dimethoxydibenzofuran in acetic acid with fuming nitric acid. The structure of the nitro compound was established by reduction to the corresponding amino compound. An intimate mixture of this compound and an authentic specimen of 1-amino-3,4-dimethoxydibenzofuran prepared from the known 1-bromo-3,4-dimethoxydibenzofuran[20] exhibited no melting point depression.

Synthesis of possible antimalarial compounds.

All of these compounds contain the γ-diethylaminopropylamino group attached to the dibenzofuran nucleus. Their synthesis was carried out by heating the aminodibenzofurans with an excess of γ-diethylaminopropyl chloride hydrochloride in an oil bath at 130-165° from three to five hours. These condensations were also carried out in the presence of a solvent, such as propyl alcohol. However, in the presence of solvent, the reaction time was much longer and the yields were lower. The preparation of 3-γ-diethylaminopropylaminodibenzofuran, as shown in the following illustration, was typical of these reactions.

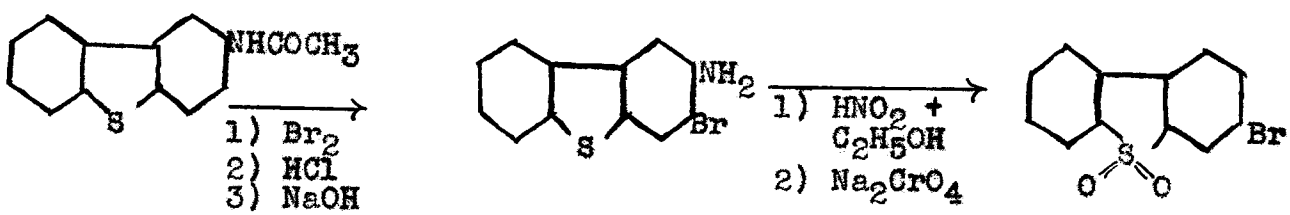


The aminodibenzofurans were condensed with γ-diethylaminopropyl chloride rather than 1-diethylamino-4-pentyl chloride (used in plasmoquin synthesis) because it is more readily

obtainable and has been shown to be at least as effective in the quinoline series. The chemotherapeutic index of plasmocide (6-methoxy-8-γ-diethylaminopropylaminoquinoline) is somewhat less than that of plasmoquin, but it is much less toxic. The compound has been tried in the clinics of the Moscow Tropical Institute and other malarial stations and is reported to have completely cured 90% of the tertian and quartan malaria and 50% of the tropical malarial cases. In fact, Fourneau[27] believes that this compound is more effective than plasmoquin, producing a quick effect in avian malaria in doses as small as 0.000003 g., and that it will eventually replace plasmoquin because it is less toxic, offers a greater margin of safety, and is less expensive to make than plasmoquin.

Dibenzothiophene

As would be expected from the study of dibenzofuran chemistry, the bromination of 2-acetaminodibenzothiophene gave 2-acetamino-3-bromodibenzothiophene.



[27] Fourneau, Bovet, et al., Ann. Inst. Pasteur, 46, 514 (1931) [C. A., 26, 3034 (1932)].

The structure of the compound was established in the following way. Hydrolysis, deamination, and oxidation of the resulting bromodibenzothiophene gave a product melting at 224-225°. A mixed melting point with an authentic specimen of 3-bromodibenzothiophene-5-dioxide[28] showed no depression. A 2-acetamino-7-bromodibenzothiophene would give the same product, but the possibility of hetero substitution was excluded on the basis of the known homonuclear directive influence of the acetamino group.

The chlorination of 2-acetaminodibenzothiophene with sulfuryl chloride proceeded smoothly to give a mono-chloro compound in 87% yield. This compound was assumed to be 2-acetamino-3-chlorodibenzothiophene by analogy with the above bromination.

The presence of a methoxyl group in the dibenzothiophene nucleus as in the dibenzofuran facilitates further substitution in the same ring. Therefore, sufficiently mild nitrating conditions may be employed to avoid attack of the sulfide linkage. Consequently, the nitration of 4-methoxydibenzothiophene with fuming nitric acid in acetic acid solution at 18-20° gave a mononitro derivative (m.p., 161-162°) in 67% yield. The sulfide linkage is not attacked under these mild conditions.

Reduction of 18 g. of the crude nitro-4-methoxydibenzothiophene (m.p., 159-161°) gave 13 g. of compound melting at 101-102° and one gram of product melting at 132-133°. By

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[28] Gilman, Jacoby, and Pacevitz, J. Org. Chem., 3, 120 (1938).

analogy with the nitration of 4-methoxydibenzofuran with fuming nitric acid (p.58) at 18-20° which gives only 1-nitro-4-methoxydibenzofuran, it was assumed that the main product (m.p., 101-102°) was 1-amino-4-methoxydibenzothiophene and the smaller fraction (m.p., 132-133°) was 3-amino-4-methoxydibenzothiophene. These structures can be ascertained by converting them to the corresponding bromo-methoxy compounds and comparing them with an authentic specimen of 1-bromo-4-methoxydibenzothiophene. The latter compound can be obtained from the known 1-bromo-4-aminodibenzothiophene through diazotization, hydrolysis, and methylation. These reactions were not carried out because of lack of time.

All of the dibenzothiophene compounds submitted for antimalarial tests, as in the dibenzofuran series, contained the γ-diethylaminopropylamino side chain. They were synthesized similarly by heating the aminodibenzothiophenes with an excess of γ-diethylaminopropyl chloride hydrochloride.

Results of Physiological Tests

All of the dibenzofuran and dibenzothiophene derivatives synthesized during the course of this investigation were sent to Parke-Davis Company, Detroit, Michigan, if they were considered to have any possible antimalarial activity. They were then relayed, by Parke-Davis Company, to cooperating laboratories

for pharmocological testing. This was carried out under the auspices of the Government of the United States. The findings from these laboratories are published only in restricted reports. Consequently, government permission must be obtained before these results are made public. The tests were designed to show if any compound possessed either therapeutic (curative) or prophylactic (preventative) value. These tests were carried out on young chicks. In the case of the therapeutic tests, the chicks were infected with the parasite first, and then fed the drug to determine its effect on the parasites already present in the blood stream; in the case of the prophylactic tests, the chicks were fed the drug first and then were infected with the parasite. The rate of increase of the parasites in the chick bloodstream was then observed. Plasmodium lophurae was the parasite most commonly used in carrying out these tests. The compound, or drug, to be tested was fed to the chicks by mixing it with the chick mash. The proportion of the compound was arranged so that the chick received from six-tenths to one gram per kilogram of body weight. The dosage was increased above this level if doubtful activity was encountered, and was decreased below this level if it was above the toxic level for the drug.

The results of the pharmocological tests on the derivatives of dibenzofuran are given in Table II. It is noticed that these compounds showed no antimalarial activity with the

TABLE II

RESULTS OF PHARMACOLOGICAL TESTS
OF DERIVATIVES OF DIBENZOFURAN

Name of Compound	No. of Test Animals	Type of Test	Daily Dose in Mgs.	Results
3-γ-Diethylaminopropyl-aminodibenzofuran	3	Thera-peutic	32	0
3-γ-Diethylaminopropyl-amino-6-iododibenzo-furan	5	Thera-peutic	30	0
2-Bromo-3-γ-diethylamino-propylaminodibenzofuran	3	Thera-peutic	15	0
2-γ-Diethylaminopropyl-aminodibenzofuran	--	--	--	--
2-γ-Diethylaminopropyl-amino-3-bromodibenzo-furan	6	Prophy-lactic	25	0
2,7-bis(γ-Diethylamino-propylamino)-dibenzo-furan	3	Thera-peutic	9	0
2,8-bis(γ-Diethylamino-propylamino)-dibenzo-furan	3	Prophy-lactic	6.5	0
4-γ-Diethylaminopropyl-aminodibenzofuran	3	Thera-peutic	31	0
1-Bromo-4-γ-diethylamino-propylaminodibenzo-furan	6	Thera-peutic	32	0

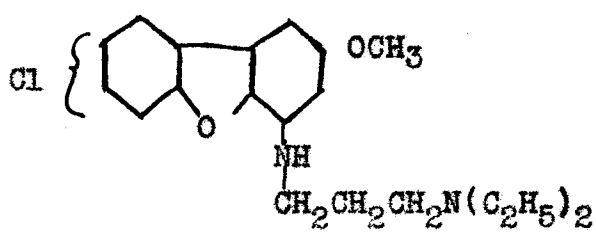
TABLE II (Continued)

Name of Compound	No. of Test Animals	Type of Test	Daily Dose in Mgs.	Results
2-Methoxy-1-γ-diethyl-aminopropylaminodibenzo-furan	5	Thera-peutic	60	0
1-γ-Diethylaminopropyl-amino-2-methoxydibenzo-furan	5	Thera-peutic	60	0
1-γ-Diethylaminopropyl-amino-4-methoxydibenzo-furan	5	Thera-peutic	60	0
1-Bromo-3-γ-diethylamino-propylamino-4-methoxydiben-zofuran	5	Thera-peutic	60	(±)
3-γ-Diethylaminopropyl-amino-4-methoxydibenzo-furan	--	--	--	--
1-γ-Diethylaminopropyl-amino-3,4-dimethoxy-dibenzofuran	5	Thera-peutic	60	0
2-Cyanodibenzofuran*	--	Thera-peutic	39	0

*Prepared by Oatfield (Oatfield, Master's Thesis, Iowa State College, (1933)).

exception of 1-bromo-3-γ-diethylaminopropylamino-4-methoxydibenzofuran, which showed a doubtful (±) activity at a daily dosage of 60 milligrams.

In spite of the negative results shown by the compounds prepared in this investigation, there is much room for additional work on the preparation and testing of dibenzofuran derivatives as antimalarial agents. Emphasis should be placed on the preparation of compounds containing three functional groups, that is, a basic side chain, methoxyl, and chloro or methyl group. The necessity of these groups is demonstrated in atabrine where the replacement of the chlorine atom with a methyl group does not markedly change the activity of the compound, but removal of the chlorine atom destroys the activity. This fact is also borne out in dibenzofuran where the only active compound was one with three functional groups, namely 1-bromo-3-γ-diethylaminopropylamino-4-methoxydibenzofuran. Compounds containing the basic side chain <u>meta</u> to the methoxyl group, as in plasmoquin, and a methyl or chloro group in the other ring will be of greatest interest. The following formula serves as an example.



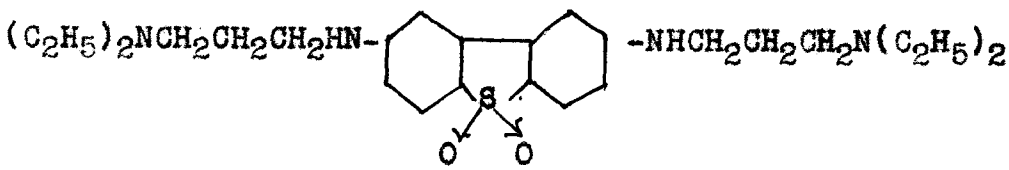
In Table III are shown the pharmocological results on the antimalarial activity of the γ-diethylaminopropylamino derivatives of dibenzothiophene. None of these derivatives showed any activity.

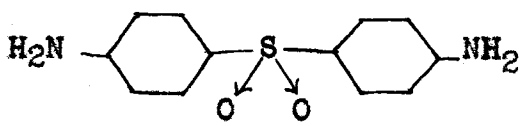
TABLE III

RESULTS OF PHARMACOLOGICAL TESTS
OF DERIVATIVES OF DIBENZOTHIOPHENE

Name of Compound	No. of Test Animals	Type of Test	Daily Dose in Mgs.	Results
2-γ-Diethylaminopropyl-aminodibenzothiophene	4	Thera-peutic	5	0
2-γ-Diethylaminopropyl-amino-3-bromodibenzo-thiophene	5	Thera-peutic	30	0
2-γ-Diethylaminopropyl-amino-3-chlorodibenzo-thiophene	2	Thera-peutic	10	0
4-γ-Diethylaminopropyl-aminodibenzothiophene	4	Thera-peutic	19	0
1-Bromo-4-γ-diethylamino-propylaminodibenzo-thiophene	1	Thera-peutic	27	0
1-γ-Diethylaminopropyl-amino-4-methoxydibenzo-thiophene	1	Prophy-lactic	22	0

The number of dibenzothiophene derivatives prepared and tested is too few to determine whether the dibenzothiophene nucleus is suitable or not for antimalarial synthesis. Consequently, additional compounds should be prepared and tested to determine its effectiveness. Special emphasis should be placed on the preparation of the oxidized derivatives of dibenzothiophene for reasons outlined on page 12. A compound of considerable interest would be one containing two γ-diethylaminopropylamino groups para to the sulfide linkage. A compound of this type will be a so-called closed model derivative of 4,4'-diaminodiphenyl sulfone.





While the preparation of 4,4'-bis-(γ-diethylaminopropylamino) diphenyl sulfone has not been reported in the open literature, the dextrose sulfonate of 4,4'-diaminodiphenyl sulfone has been demonstrated by Coggeshall[18] to be effective in human malaria.

EXPERIMENTAL

Dibenzofuran

4,6-Diiododibenzofuran.

The preparation of 4,6-diiododibenzofuran in 19% yield by reacting 4,6-disodiodibenzofuran with iodine was accomplished by R. V. Young.[29] However, the low yields obtained, the time involved, and the prohibitive cost of butylsodium made his method impractical. Therefore, his experimental conditions were changed and the method of O. Baine,[30] with slight modifications for dimetalation of dibenzofuran with benzylsodium, was used.

In accordance with Pacevitz's[31] procedure, phenylsodium was prepared by placing a mixture of 1200 cc. of toluene, 115 g. (5.0 g. atom) of sodium sand, and 225 g. (2.0 moles) of chlorobenzene in a three liter 3-necked round-bottomed flask equipped with a Hopkins condenser having a nitrogen inlet, a mercury-sealed stirrer, and a thermometer. A small crystal of iodine was introduced as a catalyst. Five minutes after the addition,

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[29] Gilman and Young, J. Am. Chem. Soc., 54, 1121 (1935).

[30] Gilman, Moore, and Baine, ibid., 63, 2479 (1941).

[31] Gilman, Pacevitz, and Baine, ibid., 62, 1514 (1940).

the temperature began to rise and by appropriate cooling was not allowed to exceed 55° during the entire reaction period, which lasted about four hours.

A solution of 168 g. (1.0 mole) of dibenzofuran in 800 cc. of toluene was added all at once to the above mixture and the temperature raised to 100-105° by means of an oil bath. The reaction mixture was stirred at this temperature for twelve hours. At the end of this period, the mixture was cooled in an ice-salt bath (-15°) and 635 g. (2.5 moles) of iodine was added at such a rate as to keep the temperature below 12°. The reaction was completed by heating to 60-65° for one hour. The mixture was filtered, washed with 400 cc. of water containing 10 g. of sodium thiosulfate, and dried over calcium chloride. Concentration of the solvent to 300 cc. yielded 290 g. of crude product, m.p., 155-158°. One crystallization from toluene yielded colorless crystals melting sharply at 160°. The yield of the pure 4,6-diiododibenzofuran was 256 g. or 60.1%.

In three other runs, the product was obtained in yields of 59%, 57%, and 61%.

Amination of 4,6-diiododibenzofuran.

A. With sodamide in liquid ammonia. Sodamide was prepared according to the directions of Vaughn, Vogt, and Nieuwland[32] from 10.1 g. (0.44 g. atom) of sodium and 0.3 g. of

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[32] Vaughn, Vogt, and Nieuwland, ibid., 56, 2120 (1934).

hydrated ferric nitrate in 400 cc. of liquid ammonia. Then 84 g. (0.20 mole) of 4,6-diiododibenzofuran was added over a period of fifteen minutes. The reaction was not vigorous, and after three hours of mechanical stirring the excess sodamide was destroyed by the addition of ammonium chloride. The ammonia was allowed to evaporate and the solid was extracted with 1000 cc. of anhydrous ether. The amine was precipitated from the ether solution as the hydrochloride and then decomposed in water solution with ammonium hydroxide. Two crystallizations from methyl alcohol yielded 37.8 g. of product melting at 143-144° and 2.1 g. of product melting at 154-155°. Qualitative analysis showed that the product melting at 143-144° contained both iodine and nitrogen. This compound is probably iodo-aminodibenzofuran. The higher melting product was free of iodine.

Anal. Calcd. for $C_{12}H_8ONI$: N, 4.53. Found: N, 4.52.

Six-tenths gram (0.002 mole) of the lower melting amine was dissolved in 75 cc. of absolute ethanol, containing 1 g. of palladium-calcium carbonate catalyst, and was put under a 30-pound gauge pressure of hydrogen. The pressure dropped nearly a pound in a few minutes but the shaking was continued for half an hour in order to insure complete deiodination. The colorless solution was separated from the catalyst by filtration and the product was precipitated quantitatively when 200 cc. of water was added slowly to the alcoholic solution. After one recrystallization from dilute methanol, the product melted at

95-96°. A mixed melting point with 3-aminodibenzofuran showed no depression. This established the position of the amino group.

Three grams (0.01 mole) of x-iodo-3-aminodibenzofuran was placed in a solution of 25 cc. of 48% sulfuric acid and 125 cc. of ethanol and warmed to 80° on a steam bath. Then a solution of 12 g. (0.174 mole) of sodium nitrite in 25 cc. of water was added dropwise with stirring. After all of the solution had been added, the mixture was refluxed gently for fifteen minutes. The contents of the flask were then cooled, filtered and subjected to steam distillation. The compound which distilled over with steam was recrystallized from methyl alcohol and melted at 73-74°. A mixed melting point with 4-iododibenzofuran showed no depression. Thus, the product melting at 143-144° must be 3-amino-6-iododibenzofuran.

The product melting at 154-155° melted at 125-130° when mixed with an authentic specimen of 4,6-diaminodibenzofuran. It is probably 3,6-diaminodibenzofuran (m.p., 152°). A melting point depression was also observed when the product was mixed with 2,7-diaminodibenzofuran (m.p., 152°), and with 3,7-diaminodibenzofuran (m.p., 150-152°).

Anal. Calcd. for $C_{12}H_{10}ON_2$: N, 14.14. Found: N, 14.26.

In a previous run, 16 g. (0.038 mole) of 4,6-diiododibenzofuran was added to a solution of sodamide, prepared from 1.8 g. (0.08 g. atom) of sodium and 180 cc. of liquid ammonia, and the reaction mixture was stirred for eight hours. The excess

sodamide was destroyed by the addition of ammonium chloride and the ammonia was allowed to evaporate. The residue was digested with dilute hydrochloric acid, filtered, and the filtrate neutralized with ammonium hydroxide. The precipitate was filtered and recrystallized from benzene to give 5 g. of product melting at 140-145°. The compound was redissolved in hot benzene and acetylated by the addition of 10 cc. of acetic anhydride. The insoluble acetyl derivative was filtered and after several crystallizations gave 1.2 g. of product melting at 320-322°, and a small amount of product melting at 267-269°. Qualitative analysis showed that the latter product contained iodine. Their structures were established when the 3-amino-6-iododibenzofuran and 3,6-diaminodibenzofuran, obtained from the above run, were acetylated to give 3-acetamino-6-iododibenzofuran (m.p., 268-269°) and 3,6-diacetaminodibenzofuran (m.p., 321-322°), respectively.

B. With sodamide in liquid ammonia and ether. Twenty-one grams (0.05 mole) of 4,6-diiododibenzofuran dissolved in 300 cc. of ether was added with stirring to a solution of 0.13 mole of sodamide in 200 cc. of liquid ammonia. The stirring was maintained for 12 hours. Excess ammonium chloride was added and the solvent was filtered free from insoluble matter. The amine was precipitated from the ether solution as the hydrochloride and then decomposed in water solution with ammonium hydroxide. A few crystallizations from methyl alcohol yielded the pure

product melting at 95-96°. A mixed melting point with 3-aminodibenzofuran showed no depression. The yield was 7.3 g. or 42%.

C. With ammonium hydroxide and cuprous bromide. Forty-two grams (0.1 mole) of 4,6-diiododibenzofuran was intimately mixed with 16 g. (0.11 mole) of cuprous bromide and placed in a glass beaker fitted as a liner for an electrically heated steel bomb, and then 190 cc. of concentrated ammonium hydroxide was added. The mixture was heated at 180-185° for twenty-eight hours. On cooling, the contents of the bomb were extracted with ether, the ether solution washed with water, and dried over anhydrous sodium sulfate. The amine was precipitated from the ether as the hydrochloride and then decomposed in water solution with ammonium hydroxide. Two crystallizations from methyl alcohol yielded 2 g. of product melting at 84.5-85°. A mixed melting point with 4-aminodibenzofuran showed no depression. The yield was 11%.

3-Acetamino-6-iododibenzofuran.

To a solution of 1.5 g. (0.005 mole) of 3-amino-6-iododibenzofuran in 20 cc. of warm benzene was added 1 cc. of acetic anhydride. The insoluble 3-acetamino-6-iododibenzofuran precipitated immediately. A quantitative yield of the crude product, m.p., 267-268°, was obtained. Crystallization from ethyl alcohol yielded small colorless needles, m.p., 268-269°.

Anal. Calcd. for $C_{14}H_{10}O_2NI$: N, 4.10. Found: N, 4.02.

3,6-Diacetaminodibenzofuran.

To a solution of one gram (0.005 mole) of 3,6-diaminodibenzofuran in 30 cc. of hot benzene was added 2 cc. of acetic anhydride. The insoluble 3,6-diacetaminodibenzofuran precipitated immediately. After 100 cc. of additional benzene had been added, the suspension was boiled, cooled, and filtered. Crystallization from acetic acid produced very small leaflets, m.p., 321-322°.

Anal. Calcd. for $C_{16}H_{14}O_3N_2$: N, 9.93. Found: N, 9.76.

4,6-Dihydroxydibenzofuran.

A. From 4,6-diiododibenzofuran. An intimate mixture of 100 g. (0.238 mole) of 4,6-diiododibenzofuran, 22 g. of copper bronze powder, and 200 g. of technical sodium hydroxide was placed in a 600 cc. copper beaker containing 100 g. of copper turnings and 30 g. of copper sulfate dissolved in 100 cc. of water. The beaker and its contents were kept at 215-220° for 15 hours in an electrically heated bomb. On cooling, the contents were transferred to a three-liter beaker, diluted with two liters of water, and brought to boiling to insure complete solution of the sodium salt. The solution was filtered, cooled, and acidified with hydrochloric acid. Filtration yielded 35 g. (or a yield of 75%) of crude 4,6-dihydroxydibenzofuran melting at 145-150°. A few crystallizations from benzene raised the

melting point to 203-204°. A mixed melting point with an authentic specimen of 4,6-dihydroxydibenzofuran[29] showed no depression. Only five grams of the above compound was purified. The remaining 30 g. were converted into 4,6-dimethoxydibenzofuran without further purification.

B. From oxidation of 4,6-dilithiodibenzofuran. Eight and four-tenths grams (0.002 mole) of 4,6-diiododibenzofuran in 75 cc. of anhydrous ethyl ether was added dropwise over a ten minute period with vigorous stirring to 0.004 mole of n-butyllithium in 75 cc. of the same solvent. After ten minutes, in accordance with the procedure of Ivanoff,[33] 0.004 mole of n-butylmagnesium bromide in 50 cc. of ether was added to improve the yield of the oxidation product. The reaction mixture was cooled below 0° in an ice-salt mixture, and oxygen (bubbled through sulfuric acid and passed over soda lime) was swept over the surface of the well stirred solution at such a rate as to maintain the temperature below zero until a negative color test[34] was obtained. The lithium salt was hydrolyzed with cold hydrochloric acid and the aqueous portion was extracted once with ether and discarded. The ether layers were combined in a separatory funnel, crushed ice was added, and extraction with 2-3% alkali was continued until no turbidity developed in an acidified

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33 Ivanoff, Bull. soc. chim., 39, 47 (1926).

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

portion. Norite was added to the alkaline solution, and dissolved ether was removed by gradual heating on a steam bath. The hot liquid was filtered, acidified, and cooled under the tap with shaking. The crude 4,6-dihydroxydibenzofuran, melting at 138-143° weighed 3.1 g. Several crystallizations from methyl alcohol yielded 0.2 g. (or 5.0%) of pure product melting at 203-204°. A mixed melting point with an authentic specimen of 4,6-dihydroxydibenzofuran showed no depression.

Methylation of 4,6-dihydroxydibenzofuran.

The procedure described here is essentially that which Cheney[20] employed to methylate 4-hydroxy-6-methoxydibenzofuran.

A 60% potassium hydroxide solution, prepared by dissolving 112.0 g. (2.80 moles) of alkali in 80 cc. of water, was added dropwise to a vigorously refluxing, stirred solution of 30.0 g. of crude 4,6-dihydroxydibenzofuran (m.p., 145-150°), 86 g. (0.682 mole) of dimethyl sulfate, and 75 cc. of acetone. The addition required one and one-half hours. Stirring at reflux temperature was continued for two hours, whereupon the product was poured into 800 cc. of water. The shiny crystals were filtered off and recrystallized from petroleum ether (b.p., 60-68°). The yield of 4,6-dimethoxydibenzofuran, melting at 128-129°, was 21 g. Cheney[28] reports the same melting point.

γ-Diethylaminopropyl chloride hydrochloride.

The procedure described here is a modification of the original procedure of Slotta and Behnisch.[35]

A mixture of 1500 cc. of chloroform and 357 g. (3.0 moles) of thionyl chloride was placed in a three-liter three-necked flask equipped with a dropping funnel, stirrer and reflux condenser. The reaction flask was immersed in an ice bath, and a solution of 200 g. (1.53 moles) of γ-diethylaminopropanol in 200 cc. of chloroform was added at such a rate as to keep the temperature between 10-15°. The mixture was stirred for fifteen minutes and then refluxed for one and one-half hours. The solvent and the excess thionyl chloride were removed by distillation. The residue was treated cautiously with 500 cc. of 40% sodium hydroxide solution and extracted with two liters of ether. The ethereal solution was dried over anhydrous sodium sulfate and then subjected to vacuum distillation. The fraction of colorless oil boiling at 170-172°/18 mm. was collected. This material weighed 165 g., which corresponds to a yield of 72%.

The base was converted to the hydrochloride by passing dry hydrogen chloride through the cold ethereal solution. The hydrochloride is a white powder and melts at 64-66°. Magidson and Strukov[36] report the melting point at 62-64°.

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35 Slotta and Behnisch, Ber., 68, 754 (1935).

36 Magidson and Strukov, Arch. Pharm., 271, 589 (1933).

3-γ-Diethylaminopropylamino-6-iododibenzofuran.

A mixture of 12.36 g. (0.04 mole) of 3-amino-6-iododibenzofuran and 9.3 g. (0.05 mole) of γ-diethylaminopropyl chloride hydrochloride was heated for three and one-half hours in a 50 cc. flask immersed in an oil bath at 160-165°. The heavy oil was dissolved in 350 cc. of hot water and then cooled to room temperature. The acidic solution was made alkaline with concentrated ammonium hydroxide, extracted with ether, and the ethereal extract dried over anhydrous sodium sulfate. The solvent was removed and the residue distilled under reduced pressure. Eleven and five tenths grams, a 68.1% yield, of a heavy yellow liquid distilling at 290-295°/ 0.5 mm. was obtained.

Anal. Calcd. for $C_{19}H_{23}ON_2I$; N, 6.62. Found: N, 6.70

3-γ-Diethylaminopropylaminodibenzofuran.

The reduction of 3-nitrodibenzofuran was carried out more conveniently in acetic acid with stannous chloride and hydrochloric acid rather than with tin and hydrochloric acid[37]. A solution of 85 g. (0.38 mole) of hydrated stannous chloride in 100 cc. of concentrated hydrochloric acid was added to a solution of 25.6 g. (0.12 mole) of 3-nitrodibenzofuran in 300 cc. of glacial acetic acid and the mixture warmed on a steam bath for twenty minutes. A brown precipitate separated and was filtered. The precipitate was titrated with an excess of 10%

[37] Cullinane, J. Chem. Soc., 2267 (1930).

sodium hydroxide solution, washed, and filtered. One crystallization from dilute ethanol yielded 20 g. (a yield of 91%) of pure 3-aminodibenzofuran.

A mixture of 12.1 g. (0.066 mole) of 3-aminodibenzofuran and 18.6 g. (0.10 mole) of γ-diethylaminopropyl chloride hydrochloride was heated in a small flask at 130° for half an hour. The mixture became semi-solid. The bath temperature was raised to 165° and kept there for three hours. The reaction product was dissolved in hot water, cooled, and filtered free from a small amount of insoluble matter. The acidic solution was made basic with concentrated ammonium hydroxide, extracted with ether, and the ethereal extract dried over anhydrous sodium sulfate. The ether was removed and the residue distilled under reduced pressure. Twelve grams, a yield of 61.7%, of light yellow oil distilling at 260-261°/0.5 mm. was obtained.

Anal. Calcd. for $C_{19}H_{24}ON_2$: N, 9.46. Found: N, 9.61.

2-Bromo-3-γ-diethylaminopropylaminodibenzofuran.

2-Bromo-3-aminodibenzofuran was prepared essentially according to the direction of Kirkpatrick[38]. Twenty grams of 3-acetaminodibenzofuran yielded 15 g. of 2-bromo-3-aminodibenzofuran.

Eight grams (0.0305 mole) of 2-bromo-3-aminodibenzofuran and 7.5 g. (0.0405 mole) of γ-diethylaminopropyl chloride hydrochloride were heated to a temperature of 150-155° for three and

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[38] Gilman, Brown, Bywater, and Kirkpatrick, J. Am. Chem. Soc., 56, 2473 (1934).

one-half hours. The reaction mixture was treated as previously described under the preparation of 3-γ-diethylaminopropylamino-6-iododibenzofuran (p. 40). The product distilled at 190-195° under a pressure of less than 0.5 mm. and was a yellow oil with a green fluorescence weighing 4.6 g., corresponding to a yield of 40.0%.

Anal. Calcd. for $C_{19}H_{23}ON_2BR$: N, 7.46. Found: N, 7.38.

The above product was also prepared by heating a mixture of 5.2 g. (0.02 mole) of 2-bromo-3-aminodibenzofuran, 7.5 g. (0.05 mole) of γ-diethylaminopropyl chloride, and 5 g. of potassium carbonate in 200 cc. of propyl alcohol at the reflux temperature for a period of twenty-four hours. The yield was very low (0.5 g. or 6.6%).

2-Nitro-3-hydroxydibenzofuran.

The 2-nitro-3-aminodibenzofuran used in this procedure was prepared according to the directions of Kirkpatrick[38].

One hundred cubic centimeters of concentrated hydrochloric acid was added to a solution of 25 g. (0.10 mole) of 2-nitro-3-aminodibenzofuran dissolved in 300 cc. of warm acetic acid. The solution was cooled to 10° and 8 g. of sodium nitrite was added in small portions with vigorous stirring. After the diazonium solution had stood for two hours in the cold, 50 g. of copper sulfide dissolved in 800 cc. of 2% sulfuric acid was added and the resulting solution was refluxed for 25 minutes. The solution

was filtered and the residue recrystallized twice from benzene. The pure 2-nitro-3-hydroxydibenzofuran, melting at 162-163°, weighed 12.0 g., a yield of 52.4%.

Anal. Calcd. for $C_{12}H_7O_4N$: N,6.11. Found: N, 6.03.

Attempted methylation of 2-nitro-3-hydroxydibenzofuran.

A 60% potassium hydroxide solution, prepared by dissolving 28 g. of alkali in 19 cc. of water, was added dropwise to a vigorously refluxing, stirred solution of 11.5 g. (0.05 mole) of 2-nitro-3-hydroxydibenzofuran, 25.2 g. (0.2 mole) of dimethyl sulfate, and 25 cc. of acetone. The addition required 35 minutes. Stirring was continued for two hours at reflux temperature, whereupon the product was poured into one liter of water. Filtration and crystallization yielded 10.5 g. of starting product. A mixed melting point with 2-nitro-3-aminodibenzofuran showed no depression.

Attempted preparation of 2-nitro-3-acetoxydibenzofuran.

Five grams of sodium acetate was added to 11.5 g. (0.05 mole) of 2-nitro-3-hydroxydibenzofuran dissolved in 50 cc. of acetic anhydride and the mixture was refluxed for three and one-half hours. Two drops of sulfuric acid was added at the end of one hour. The cool mixture was poured into 700 cc. of water and filtered as soon as most of the acetic anhydride had hydrolyzed. Crystallization from 600 cc. of ethyl alcohol yielded the starting material melting at 162-163°.

2-Nitro-3-iododibenzofuran.

Twenty-five grams (0.10 mole) of 2-nitro-3-aminodibenzofuran was diazotized by adding the well powdered amine to a solution of 8 g. of sodium nitrite in a mixture of 300 cc. of 85% phosphoric acid and 200 cc. of concentrated hydrochloric acid cooled to 0°. After two hours, the solution was diluted with 100 cc. of 45% sulfuric acid and allowed to stand for an additional hour. The excess nitrous acid was destroyed with urea, and the solution was added slowly to 30 g. of potassium iodide dissolved in 100 cc. of water. The reaction temperature was kept at 10-15° throughout the addition. The product was filtered and recrystallized from ethyl alcohol. The pure 2-nitro-3-iododibenzofuran, melting at 189-189.5°, weighed 19.0 g. This is a yield of 56%.

Anal. Calcd. for $C_{12}H_6O_3NI$: N, 4.16. Found: N, 4.10.

2-Nitro-3-dibenzofuryl-4'-methoxyphenylamine.

A mixture of 16.9 g. (0.05 mole) of 2-nitro-3-iododibenzofuran, 8.25 g. (0.05 mole) of acetyl-p-anisidine, 150 cc. of xylene, 10 g. of potassium carbonate, and 1 g. of copper bronze was stirred and refluxed for twelve hours. The mixture was filtered hot and the filtrate, upon cooling, precipitated a dark brown solid. This solid was filtered and recrystallized twice from ethyl alcohol which gave 14.1 g. (74.5%) of brown crystals melting at 154-155°.

The above acetyl compound was hydrolyzed by refluxing it for two hours in a solution of 20 g. of potassium hydroxide in 200 cc. of alcohol. The solution was then diluted with 100 cc. of hot water. On cooling 11.0 g., an 89% yield, of 2-nitro-3-dibenzofuryl-4'-methoxyphenylamine, melting at 171-173° precipitated. A further recrystallization from ethyl alcohol gave fine colorless needles melting at 173-174°.

Anal. Calcd. for $C_{18}H_{14}O_4N_2$: N, 8.38. Found: N, 8.49.

Reduction of 2-nitro-3-dibenzofuryl-4'-methoxyphenylamine.

Ten grams (0.03 mole) of 2-nitro-3-dibenzofuryl-4'-methoxyphenylamine suspended in 150 cc. of absolute ethanol was reduced with hydrogen at room temperature under forty-five pounds gauge pressure using approximately 6 cc. of an alcoholic suspension of Raney nickel catalyst. The reduction required about one hour. The catalyst was filtered and the filtrate saturated with hydrogen chloride. Dilution with ether precipitated the amine hydrochloride in a quantitative yield. The salt was converted to the free base which decomposed during crystallization from ethyl alcohol. Because of lack of time, no further attempt was made to obtain the pure amine or its hydrochloride.

2,7-bis-(γ-Diethylaminopropylamino)dibenzofuran.

Fifteen and five-tenths grams of 2,7-dinitrodibenzofuran, prepared by Cullinane's[39] method, was reduced in acetic acid through the addition of a saturated solution of stannous chloride in concentrated hydrochloric acid. The precipitate was filtered, digested with 10% sodium hydroxide solution, and filtered. One crystallization from ethyl alcohol yielded 10.0 g. (92%) of pure 2,7-diaminodibenzofuran melting at 145-146°.

A mixture of 7.0 g. (0.0356 mole) of 2,7-diaminodibenzofuran and 18.60 g. (0.10 mole) of γ-diethylaminopropyl chloride hydrochloride was heated for three hours under an atmosphere of nitrogen at 160-165°. The reaction mixture was treated as previously described under the preparation of 3-γ-diethylaminopropylaminodibenzofuran (p. 40). The product distilled at 285-290°/0.10 mm. and was a yellow oil with fluorescence weighing 10.1 g., corresponding to a yield of 66.8%.

Anal. Calcd. for $C_{26}H_{40}ON_4$: N, 13.20. Found: N, 13.40.

2,8-bis-(γ-Diethylaminopropylamino)dibenzofuran.

The 2,8-diaminodibenzofuran was prepared by amination of 2,8-dibromodibenzofuran according to Swislowsky's[22] procedure.

A mixture of 7.0 g. (0.0356 mole) of 2,8-diaminodibenzofuran,

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39 Cullinane, J. Chem. Soc., 2365 (1932).

14.9 g. (0.1 mole) of γ-diethylaminopropyl chloride, 300 cc. of propyl alcohol, and 5.2 g. (0.72 mole) of fused sodium acetate was stirred and refluxed for twenty-four hours. The solution was diluted with water, made acid with 10 cc. of concentrated hydrochloric acid and the alcohol evaporated under partially reduced pressure. Two hundred cubic centimeters of water was added and the small amount of insoluble material filtered. The filtrate was made basic with ammonium hydroxide, extracted with ether, and the ethereal solution dried over anhydrous sodium sulfate. The ether was removed and the residue distilled under reduced pressure. Eight and two-tenths grams, a yield of 54.1%, of reddish oil distilling at 240-245°/0.1 mm. was obtained.

Anal. Calcd. for $C_{26}H_{40}ON_4$: N, 13.20. Found: N, 12.99.

Attempted preparation of 2-α-methyl-δ-diethylaminobutylaminodibenzofuran.

In accordance with the direction of Gilman and co-workers[38], a solution of 16.8 g. (0.10 mole) of dibenzofuran, 12.7 g. (0.10 mole) of iodine, and 7 cc. of concentrated nitric acid dissolved in 100 cc. of chloroform was stirred and refluxed for four hours. The 2-iododibenzofuran melted at 112-113° after two crystallizations from ethyl alcohol.

A mixture of 8.8 g. (0.030 mole) of 2-iododibenzofuran and 9.60 g. (0.06 mole) of 1-diethylamino-4-aminopentane was heated at 180-200° for 48 hours. At the end of this period, the mixture began to reflux and in a few hours the reflux temperature dropped

to 145°. The mixture was cooled and recrystallized from ethyl alcohol. The 2-iododibenzofuran was recovered quantitatively.

2-Bromodibenzofuran.

2-Bromodibenzofuran has been prepared by Bywater[23] in 20-25% yields by brominating dibenzofuran in carbon tetrachloride. The reaction period has been shortened and the yields improved by carrying out the reaction under the radiation of a quartz jacketed H-4 mercury-vapor lamp.

A solution of 168 g. (1.0 mole) of dibenzofuran in 600 cc. of carbon tetrachloride was placed in a one liter three-necked flask fitted with a reflux condenser, dropping funnel, and a mechanical stirrer. The solution was exposed to the radiation from a quartz jacketed H-4 mercury-vapor lamp and 160 g. (1.0 mole) of bromine was added with stirring over a period of three hours. Irradiation was continued for two more hours at room temperature and finally for one hour at the reflux temperature of carbon tetrachloride. Subsequent to the removal of the carbon tetrachloride by distillation, the product was distilled under reduced pressure to give 151 g., or a 61% yield of 2-bromodibenzofuran melting at 102-106°. One crystallization from petroleum ether (b.p., 60-68°) yielded 128 g. (51%) of pure product melting at 108-109°. A mixed melting point with an authentic specimen of 2-bromodibenzofuran showed no depression.

2-γ-Diethylaminopropylaminodibenzofuran.

2-Aminodibenzofuran was prepared by high temperature and pressure amination of the corresponding bromo-compound in accordance with Bywater's[38] directions.

A mixture of 12.1 g. (0.066 mole) of 2-aminodibenzofuran, 14.9 g. (0.10 mole) of γ-diethylaminopropyl chloride, 250 cc. of propyl alcohol, and 7.0 g. of fused sodium acetate was stirred for 18 hours. The alcohol was evaporated under reduced pressure, the residue digested with dilute hydrochloric acid, and filtered free from a small amount of insoluble matter. The filtrate was made basic with ammonium hydroxide, extracted with ether, and the ethereal solution dried over anhydrous sodium sulfate. The ether was removed and the residue distilled under reduced pressure. Eleven grams, a yield of 64%, of reddish oil distilling at 185-190°/2 mm. was obtained.

Anal. Calcd. for $C_{19}H_{24}ON_2$: N, 9.46. Found: N, 9.57.

2-Acetamino-3-bromodibenzofuran.

W. G. Bywater[38] prepared 2-acetamino-3-bromodibenzofuran by bromination of 2-diacetaminodibenzofuran. P. R. Van Ess[26] prepared the same compound in 16.4% yield by brominating 2-acetaminodibenzofuran in acetic acid. The author prepared the same compound in 36% yield by brominating 2-acetaminodibenzofuran in chloroform.

Bromination of 2-acetaminodibenzofuran, prepared by treatment of the amine with acetic anhydride in benzene solution[38], was affected by adding 100 cc. of a molar solution of bromine in chloroform to a solution of 22.5 g. (0.10 mole) of 2-acetaminodibenzofuran in 300 cc. of chloroform at room temperature. After standing for two hours, the precipitate was filtered and the solution was diluted with 300 cc. of ethyl alcohol. The mixture was refluxed for a few minutes, cooled to room temperature, and filtered. The precipitates were combined and recrystallized from acetic acid. The yield of the pure 2-acetamino-3-bromodibenzofuran, m.p., 240-241°, was 11.0 g. or 36%.

2-γ-Diethylaminopropylamino-3-bromodibenzofuran.

The 2-amino-3-bromodibenzofuran was prepared by the alkaline hydrolysis of 2-acetamino-3-bromodibenzofuran[26].

Eight grams (0.0305 mole) of 2-amino-3-bromodibenzofuran and 7.50 g. (0.0405 mole) of γ-diethylaminopropyl chloride hydrochloride were heated to a temperature of 166-170° for three hours. The reaction mixture was treated as previously described under the preparation of 3-γ-diethylaminopropylamino-6-iododibenzofuran (p. 40). The product distilled at a bath temperature of 200-216° under a pressure of less than 0.5 mm. and was a reddish oil with slight fluorescence weighing 3.4 g., corresponding to a yield of 30%.

Anal. Calcd. for $C_{19}H_{23}ON_2Br$: N, 7.46. Found: N, 7.51.

The above product was also prepared by heating 5.2 g. (0.02 mole) of 2-amino-3-bromodibenzofuran, 7.5 g. (0.05 mole) of γ-diethylaminopropyl chloride, and five grams of sodium acetate in 150 cc. of absolute ethyl alcohol at the reflux temperature for a period of 15 hours. The yield was extremely low.

2-Methoxy-3-nitrodibenzofuran.

The 2-methoxydibenzofuran was prepared according to the directions of Gilman and Van Ess[26].

Ten grams (0.05 mole) of 2-methoxydibenzofuran was dissolved in 150 cc. of glacial acetic acid and cooled to 15°. Eight cubic centimeters of fuming nitric acid (sp. g., 1.49) was added dropwise with stirring, during a period of five minutes. The mixture was kept at 15-18° for 10 minutes and then filtered. The precipitate was washed with several cubic centimeters of acetic acid and then with water. The dry product, melting at 185-186°, weighed 9.0 g., a 73% yield. One crystallization from ethyl alcohol raised the melting point to 186-186.5°.

Analysis showed the substance to be a mononitro derivative later proved to be 2-methoxy-3-nitrodibenzofuran.

Anal. Calcd. for $C_{13}H_9O_4N$: N, 5.76. Found: N, 5.73.

2-Methoxy-3-aminodibenzofuran.

A solution of 59.5 g. (0.268 mole) of hydrated stannous chloride in 70 cc. of concentrated hydrochloric acid was added to a suspension of 20.0 g. (0.0816 mole) of 2-methoxy-3-nitrodibenzofuran in 300 cc. of acetic acid and the mixture heated on the water bath for one hour. The brown precipitate was filtered, digested with an excess of 10% sodium hydroxide solution, washed and filtered. One crystallization from methyl alcohol produced 15.0 g. (87.0%) of pure 2-methoxy-3-aminodibenzofuran melting at 92-92.5°.

Anal. Calcd. for $C_{13}H_{11}O_2N$: N, 6.57. Found: N, 6.62.

One gram (0.005 mole) of 2-methoxy-3-aminodibenzofuran was diazotized by adding the well powdered amine to a solution of 0.34 g. of sodium nitrite in 50 cc. of 1:1 hydrochloric acid cooled to -5°. After 10 minutes, the clear solution was added in small portions to a boiling solution of 1.5 g. (0.01 mole) of cuprous bromide in 10% hydrobromic acid solution. After the addition was completed, the mixture was refluxed for twenty minutes. The precipitate was filtered and recrystallized twice from benzene. The pure product melted at 172° and showed no depression when mixed with an authentic sample of 2-methoxy-3-bromodibenzofuran[26].

2-Methoxy-3-γ-diethylaminopropylaminodibenzofuran.

A mixture of 11 g. (0.0518 mole) of 2-methoxy-3-aminodibenzofuran and 15.0 g. (0.10 mole) of γ-diethylaminopropyl chloride was heated under an atmosphere of nitrogen at 150-155°. After four hours, the reaction product was dissolved in 300 cc. of water, filtered, made basic with concentrated ammonium hydroxide, and extracted with ethyl ether. The ethereal solution was dried over sodium sulfate. Evaporation of the ether and distillation of the residue under reduced pressure, yielded 12 g. of yellow oil boiling at 210-213°/ 0.10 mm. This constitutes a 71.0% yield.

Anal. Calcd. for $C_{20}H_{26}O_2N_2$: N, 8.58. Found: N, 8.52.

1-Amino-2-methoxydibenzofuran.

1-Bromo-2-methoxydibenzofuran was prepared according to the directions of Gilman and Van Ess[26] by methylating 1-bromo-2-hydroxydibenzofuran, which in turn was prepared by brominating 2-hydroxydibenzofuran in acetic acid.

The α-methylhydroxylamine used in the following reaction was prepared by adding 39 cc. of 60% potassium hydroxide to 21 g. (0.25 mole) of α-methylhydroxylamine hydrochloride suspended in 400 cc. of ether. The ether-amine solution distilled over at 34-36°. A few grams of the methylhydroxylamine came over at 49-50° after all of the ether had distilled. The two fractions

were mixed and the ethereal solution was dried over anhydrous sodium sulfate.

The Grignard reagent of 33.0 g. (0.12 mole) of 1-bromo-2-methoxydibenzofuran was prepared in the customary manner by reacting a mixture of 33.0 g. (0.12 mole) of the halide, 6.3 g. (0.25 g. atom) of magnesium turnings in a mixture of 150 cc. of anhydrous ether and 150 cc. of dry benzene. In order to start the reaction, it was necessary to add a little methyl iodide. After refluxing for two hours, the solution was cooled to 0° and 1.9 g. (0.04 mole) of α-methylhydroxylamine, dissolved in 65 cc. of ether, was added over a ten minute period. The solution became brown during the addition of the amine solution and a flocculent precipitate settled. The ice-bath was removed and the mixture refluxed for one-half hour to make certain that the reaction was completed. The solution was cooled again in an ice-salt bath and carefully hydrolyzed by the very slow addition of 200 cc. of dilute hydrochloric acid with vigorous stirring. The ether-benzene layer was separated and aqueous solution extracted twice with 50 cc. portions of ether. The combined extracts were dried and then dry hydrogen chloride gas was passed in to precipitate the amine hydrochloride. When the solution was saturated with hydrogen chloride, the amine hydrochloride was filtered off and suspended in a liter of dilute ammonium hydroxide solution. The free amine was filtered and recrystallized from dilute ethyl alcohol. The yield of the pure product, melting at 92.5°, was 5.8 g. or 68% (based on the α-methylhydroxylamine).

Anal. Calcd. for $C_{13}H_{11}O_2N$: N, 6.57. Found: N, 6.65.

1-γ-Diethylaminopropylamino-2-methoxydibenzofuran.

A mixture of 5.5 g. (0.0258 mole) of 1-amino-2-methoxydibenzofuran and 7 g. (0.0376 mole) of γ-diethylaminopropyl chloride hydrochloride was heated at 150-155° for three hours and then at 165° for one hour. The reaction mixture was dissolved in warm water and worked up as previously described under the preparation of 3-γ-diethylaminopropylaminodibenzofuran (p. 40). The product distilled at 205-207°/0.1 mm. and was a yellow oil with fluorescence weighing 6.7 g., corresponding to a yield of 80%.

Anal. Calcd. for $C_{20}H_{26}O_2N_2$: N, 8.58. Found: N, 8.54.

Reactions of 1-bromo-2-methoxydibenzofuran with sodamide.

Fourteen grams (0.0505 mole) of 1-bromo-2-methoxydibenzofuran dissolved in 300 cc. of anhydrous ether was added with stirring to a solution of 0.06 mole of sodamide in 100 cc. of liquid ammonia. The stirring was maintained for one hour. Excess ammonium chloride was added and the solvent was filtered free from insoluble matter. The amine was precipitated from the ether solution as the hydrochloride and then decomposed in water solution with ammonium hydroxide. One crystallization from ethyl alcohol gave a product melting at 165-166°. Two crystallizations from alcohol followed by three crystallizations

from benzene failed to raise the melting point. This was not the expected 1-amino-2-methoxydibenzofuran. Apparently some rearrangement had taken place. The product contained a very small amount of bromine as impurity which could not be removed by crystallization.

Anal. Calcd. for $C_{13}H_{11}O_2N$: N, 6.57. Found: N, 5.7, 5.8.

4-Iododibenzofuran.

The preparation of 4-iododibenzofuran in 30% yield by reacting iodine with 4-dibenzofurylmercuric acetate was accomplished by Young[40]. It was found that the more conveniently prepared 4-dibenzofuryllithium could also be used.

A solution of 16.8 g. (0.10 mole) of dry dibenzofuran in 50 cc. of ether was metalated by an excess of n-butyllithium in 75.0 cc. of ether, by refluxing and stirring for sixteen to eighteen hours in a nitrogen atmosphere. The reaction mixture was cooled in an ice-salt bath and 25.4 g. (0.1 mole) of iodine was added at such a rate as to keep the temperature below 5°. The mixture was refluxed for half an hour to make certain that the reaction was completed. The inorganic matter was dissolved in water, and the ether layer was separated and dried over sodium sulfate. Evaporation of the ether yielded a brownish solid melting at 63-65°. Two crystallizations from petroleum

[40] Gilman and Young, J. Am. Chem. Soc., 56, 1415 (1934).

ether (b.p., 60-68°) raised the melting point to 72-73°. A mixed melting point with Young's[40] sample showed no depression. The yield was 12 g. (42%).

Attempted preparation of 4-1'-methyl-4'-diethylaminobutylaminodibenzofuran.

A mixture of 8.8 g. (0.030 mole) of 4-iododibenzofuran and 9.60 g. (0.06 mole) of 1-diethylamino-4-aminopentane was heated at 180-200° for 36 hours. At the end of this period, the bath temperature had to be lowered since the mixture began to reflux rather vigorously and after a few hours began to reflux at 135-140°. The reaction mixture was digested with dilute hydrochloric acid and filtered. Crystallization from petroleum ether (b.p., 60-68°) yielded 7.6 g. of 4-iododibenzofuran.

4-γ-Diethylaminopropylaminodibenzofuran.

The necessary 4-aminodibenzofuran was prepared by reacting an ethereal solution of 4-dibenzofuryllithium with -methylhydroxylamine, in accordance with Willis' directions[41].

A mixture of 6.0 g. (0.033 mole) of 4-aminodibenzofuran and 7.5 g. (0.05 mole) of γ-diethylaminopropyl chloride was heated for three hours under an atmosphere of nitrogen at 145-150°. The reaction mixture was treated as previously described under the preparation of 3-γ-diethylaminopropylaminodibenzofuran (p. 40).

[41] Willis, Doctoral Dissertation, Iowa State College (1943).

Eight grams, a yield of 82%, of light yellow oil distilling at 210-213°/0.5 mm. was obtained.

Anal. Calcd. for $C_{19}H_{24}ON_2$: N, 9.46. Found: N, 9.64.

1-Bromo-4-γ-diethylaminopropylaminodibenzofuran.

1-Bromo-4-aminodibenzofuran was prepared essentially according to the direction of Van Ess[26]. Eleven grams of 4-acetaminodibenzofuran yielded 8 g. of 1-bromo-4-aminodibenzofuran.

Eight grams (0.0305 mole) of 1-bromo-4-aminodibenzofuran and 7.5 g. (0.04 mole) of γ-diethylaminopropyl chloride hydrochloride were heated to a temperature of 160-165° for three hours. The reaction mixture was treated as previously described under the preparation of 3-γ-diethylaminopropylaminodibenzofuran (p. 40). The product distilled at 212-215° under a pressure of less than 0.1 mm. and was a light yellow oil with a green fluorescence weighing 4.5 g., corresponding to a yield of 40.0%.

Anal. Calcd. for $C_{19}H_{23}ON_2Br$: N, 7.46. Found: N, 7.50.

1-Nitro-4-methoxydibenzofuran.

1-Nitro-4-methoxydibenzofuran has been prepared in 18% yield by nitrating 4-methoxydibenzofuran in acetic anhydride with fuming nitric acid[42]. It was found that the nitration

[42] Gilman, Jacoby, and Swislowsky, J. Am. Chem. Soc., 61, 954 (1939).

could be carried out more conveniently in acetic acid.

Twenty seven and seven tenths grams (0.14 mole) of 4-methoxydibenzofuran was dissolved in 200 cc. of glacial acetic acid and cooled to 20°. Twenty cubic centimeters of fuming nitric acid (sp. g., 1.49) was added with stirring over a period of ten minutes. The mixture was kept at 18-20° for fifteen minutes and filtered. The precipitate was washed with 25 cc. of acetic acid and then with water. The dry product, melting at 152-153°, weighed 18 g. (a 53% yield). One crystallization from ethyl alcohol gave the pure product melting at 153.5-154°. A mixed melting point with Jacoby's[42] compound showed no depression.

1-γ-Diethylaminopropylamino-4-methoxydibenzofuran.

A solution of 60.0 g. (0.267 mole) of hydrated stannous chloride in 70 cc. of concentrated hydrochloric acid was added to a suspension of 18.0 g. (0.0741 mole) of 1-nitro-4-methoxydibenzofuran in 250 cc. acetic acid and the mixture heated on the water bath. After twenty minutes, a clear solution resulted. The heating was continued for 30 minutes longer. On cooling, a white precipitate separated and was filtered. The precipitate was treated with an excess of 25% sodium hydroxide solution, filtered, and the precipitate recrystallized from dilute ethanol. The yield of the pure 1-amino-4-methoxydibenzofuran, melting at 103-104°, was 14.5 g. or 92%.

A mixture of 5.5 g. (0.0258 mole) of 1-amino-4-methoxydibenzofuran and 7.0 g. (0.0376 mole) of γ-diethylaminopropyl chloride hydrochloride was heated at 160-165° for five hours and then at 170° for one-half hour. A slow current of nitrogen was swept over the mixture throughout the reaction. The reaction mixture was dissolved in water and worked up in the usual manner. Six and five-tenths grams (an 80% yield) of yellow oil distilled at 211-215°/0.1 mm.

Anal. Calcd. for $C_{20}H_{26}O_2N_2$: N, 8.58. Found: N, 8.66.

1-Bromo-3-γ-diethylaminopropylamino-4-methoxydibenzofuran.

The necessary 1-bromo-3-amino-4-methoxydibenzofuran was prepared according to Parker's[43] directions by nitrating 1-bromo-4-methoxydibenzofuran and reducing the nitro product with stannous chloride in acetic acid.

A mixture of 8.8 g. (0.03 mole) of 1-bromo-3-amino-4-methoxydibenzofuran and 7.5 g. (0.04 mole) γ-diethylaminopropyl chloride hydrochloride was heated under a nitrogen atmosphere at 160-165°. After three hours, the bath was removed and the dark brown oil was poured into one liter of water. The water was brought to a boil and filtered from a considerable amount of insoluble matter. The cold filtrate was made basic with concentrated ammonium hydroxide and extracted with two liters of ethyl ether. A considerable amount of black ether insoluble

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[43] Gilman, Parker, Bailie, and Brown, ibid., 61, 2836 (1939).

matter was filtered and the ether dried over sodium sulfate. The ether was evaporated and the residue distilled at reduced pressure. Three and two-tenths grams of dark red oil, a yield of 25.8%, distilled over at 245-250°/0.1 mm.

Anal. Calcd. for $C_{20}H_{25}O_2N_2Br$: N, 6.94. Found: N, 6.96.

3-γ-Diethylaminopropylamino-4-methoxydibenzofuran.

In accordance with Parker's[43] directions, five grams of 1-bromo-3-nitro-4-methoxydibenzofuran was suspended in 300 cc. of absolute alcohol with 15 g. of palladium-calcium carbonate catalyst and shaken with hydrogen under a gauge pressure of 35 pounds for thirty minutes at room temperature. Filtration and dilution of the alcohol with 100 cc. of water yielded 2.5 g. of 3-amino-4-methoxydibenzofuran.

A mixture of 2.3 g. (0.013 mole) of 3-amino-4-methoxydibenzofuran and 5.0 g. (0.026 mole) of γ-diethylaminopropyl chloride hydrochloride was heated at 150-155° over a three hour period. The reaction product was dissolved in water and worked up as previously described under the preparation of 3-γ-diethylaminopropylaminodibenzofuran (p. 40). The product distilled at 231-234°/0.3 mm. and was a red oil weighing two grams, corresponding to a yield of 50%.

Anal. Calcd. for $C_{20}H_{26}O_2N_2$: N, 8.58. Found: N, 8.71.

1-Nitro-3,4-dimethoxydibenzofuran.

The 3,4-dimethoxydibenzofuran was prepared according to Cheney's[20] directions by methylating 3-hydroxy-4-methoxydibenzofuran obtained from the oxidation of a mixture of 4-methoxy-6-dibenzofuryllithium and 4-methoxy-3-dibenzofuryllithium.

Nine grams (0.0394 mole) of 3,4-dimethoxydibenzofuran was dissolved in 100 cc. of warm acetic acid and cooled to room temperature. Nine cubic centimeters of fuming nitric acid (sp. g., 1.49) was added with stirring and cooling over a period of five minutes. A heavy yellow precipitate separated at once. The mixture was kept under tap water for ten minutes and then filtered. The precipitate was washed first with a little acetic acid and then with water. One crystallization from acetic acid yielded 10.5 g. (96%) of pure product melting at 146-147°.

Analysis showed the substance to be a mononitroderivative later proved to be 1-nitro-3,4-dimethoxydibenzofuran.

Anal. Calcd. for $C_{14}H_{11}O_5N$: N, 5.12. Found: N, 5.11.

1-Amino-3,4-dimethoxydibenzofuran.

Eight grams (0.0292 mole) of the above nitro compound suspended in 200 cc. of absolute ethanol was reduced with hydrogen at room temperature under forty pounds gauge pressure using approximately 6 cc. of an alcoholic suspension of Raney nickel catalyst. The reduction required about an hour. The catalyst was filtered and the filtrate saturated with dry hydrogen

chloride. Dilution with ether precipitated the amine hydrochloride in quantitative yield. The salt was suspended in water and decomposed with concentrated ammonium hydroxide. One crystallization from petroleum ether (b.p., 60-68°) yielded 6.5 g. (92%) of pure product melting at 162-163°. A mixed melting point with the authentic 1-amino-3,4-dimethoxydibenzofuran[20] showed no depression.

1-γ-Diethylaminopropylamino-3,4-dimethoxydibenzofuran.

A mixture of 5.1 g. (0.025 mole) of 1-amino-3,4-dimethoxydibenzofuran and 7.0 g. (0.0376 mole) of γ-diethylaminopropyl chloride hydrochloride was heated at 150° for one hour and then at 175° for three hours. A slow current of nitrogen was swept over the mixture throughout the reaction. The reaction mixture was dissolved in water and worked up in the usual manner. The product distilled at 240-243° under a pressure of less than 0.1 mm. and was a light yellow oil with a green fluorescence weighing 4.5 g., corresponding to a yield of 50.5%. The product is rather unstable toward oxidation and turns blue on exposure to air.

Anal. Calcd. for $C_{21}H_{28}O_3N_2$: N, 7.88. Found: N, 7.97.

Dibenzothiophene

2-γ-Diethylaminopropylaminodibenzothiophene.

A solution of 85 g. (0.38 mole) of hydrated stannous chloride in 100 cc. of concentrated hydrochloric acid was added to a solution of 22.5 g. (0.10 mole) of 2-nitrodibenzothiophene[44] in 300 cc. of glacial acetic acid and the mixture warmed on a steam bath for one-half hour. A dark precipitate separated and was filtered. The precipitate was digested with an excess of 10% sodium hydroxide solution, washed and filtered. One crystallization from dilute ethanol yielded 17.0 g. (an 87% yield) of pure 2-aminodibenzothiophene melting at 133°.

A mixture of 6.0 g. (0.03 mole) of 2-aminodibenzothiophene and 9.3 g. (0.05 mole) of γ-diethylaminopropyl chloride hydrochloride was heated in a small flask at 145-150° for three hours. The reaction mixture was dissolved in hot water, cooled, and filtered free from a small amount of insoluble matter. The acidic solution was made basic with concentrated ammonium hydroxide, extracted with ether and the ethereal extract dried over sodium sulfate. The ether was evaporated and the residue distilled under reduced pressure. Eight grams, an 85.2% yield, of light yellow oil distilling at 280-282°/2.0 mm. was obtained.

Anal. Calcd. for $C_{19}H_{24}N_2S$: N, 9.00. Found: N, 9.16

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[44] Cullinane, Davies, and Davies, J. Chem. Soc., 1435 (1936).

2-Acetamino-3-bromodibenzothiophene.

Ten grams (0.042 mole) of 2-acetaminodibenzothiophene was dissolved in 200 cc. of glacial acetic acid and treated with 44 cc. of a 0.1 molar solution of bromine in acetic acid. The addition required 30 minutes and the solution was then stirred an additional hour before pouring into 500 cc. of water to which a little sodium bisulfite had been added. The precipitated solid, melting at 197-198°, weighed 10.0 g. and represented a 74% yield. Two recrystallizations from ethyl alcohol gave the pure product melting at 199-200°.

Analysis showed the substance to be a monobromo derivative later proved to be 2-acetamino-3-bromodibenzothiophene.

Anal. Calcd. for $C_{14}H_{10}ONSBr$: N, 4.38. Found: N, 4.41.

2-Amino-3-bromodibenzothiophene.

To 6.4 g. (0.02 mole) of 2-acetamino-3-bromodibenzothiophene in 300 cc. of 95% ethanol was added 300 cc. of concentrated hydrochloric acid and the mixture was refluxed on a steam bath. A clear solution resulted upon the addition of the hydrochloric acid, but a precipitate began to form after about thirty minutes. The refluxing was continued for two hours. The precipitated hydrochloride was filtered, suspended in water, and decomposed with ammonium hydroxide. One crystallization from ethyl alcohol yielded 5.0 g. (90%) of the pure product melting at 135-135.5°.

Anal. Calcd. for $C_{12}H_8NSBr$: N, 5.04. Found: N, 5.11.

3-Bromodibenzothiophene-5-dioxide.

The procedure used for deamination was essentially that of Cullinane[39]. To a solution of 0.5 g. (0.0018 mole) of 2-acetamino-3-bromodibenzothiophene in 15 cc. of alcohol was added cautiously a mixture of 4 cc. of concentrated sulfuric acid in 2 cc. of water. While the resulting solution was kept at 80°, 1.2 g. of sodium nitrite was added slowly. The reaction was then completed by refluxing for 20 minutes. Dilution of the reaction mixture with water, and cooling, gave a red solid which was filtered, washed with dilute sodium hydroxide, and then washed with water.

The above dry crude product was added to a cold solution of 14 cc. of glacial acetic acid, 5 drops of concentrated sulfuric acid, 5 drops of water and 0.1 g. of sodium dichromate. The reaction mixture was refluxed for one-half hour, cooled, diluted with water, and filtered. Recrystallization from ethanol yielded a small amount of product melting at 224-225°. A mixed melting point with 3-bromodibenzothiophene-5-dioxide[28] showed no depression.

2-γ-Diethylaminopropylamino-3-bromodibenzothiophene.

A mixture of 4.5 g. (0.0163 mole) of 2-amino-3-bromodibenzothiophene and 6.0 g. (0.0322 mole) of γ-diethylaminopropyl chloride hydrochloride was heated in a small flask at 155-160°. After three hours, the reaction mixture was dissolved in water

and treated as previously described under the preparation of 2-γ-diethylaminopropylaminodibenzothiophene (p. 64). Two and eight-tenths grams (a 44% yield) of reddish oil distilled over at 275-280°/0.5 mm.

Anal. Calcd. for $C_{19}H_{23}N_2SBr$: N, 7.16. Found: N, 6.93.

2-Acetamino-3-chlorodibenzothiophene.

To seventeen grams (0.0708 mole) of 2-acetaminodibenzothiophene dissolved in 300 cc. of chloroform was added, dropwise, 71 cc. of a tenth molar solution of sulfuryl chloride in chloroform. The reaction was carried out at room temperature and the solution was stirred mechanically. When about one-third of the sulfuryl chloride had been added, a white crystalline precipitate began to form; addition of the sulfuryl chloride required 30 minutes. The mixture was allowed to stand for one hour and then filtered with suction. The precipitated material weighed 17 g. (an 87% yield) and melted at 194-196°. One crystallization from ethanol gave the pure product melting at 199.5-200°. This compound was assumed to be 2-acetamino-3-chlorodibenzothiophene by analogy with the bromination of 2-acetaminodibenzothiophene which gives 2-acetamino-3-bromodibenzothiophene.

Anal. Calcd. for $C_{14}H_{10}ONSCl$: N, 5.08. Found: N, 5.12.

2-Amino-3-chlorodibenzothiophene.

Thirteen and eight-tenths grams (0.05 mole) of 2-acetamino-3-chlorodibenzothiophene was refluxed with 150 cc. of concentrated hydrochloric acid and 150 cc. of 95% ethanol. A heavy precipitate began to form after one-half hour. The refluxing was continued for two hours. The precipitated hydrochloride was filtered, suspended in water, and decomposed with ammonium hydroxide. Filtration gave 10.5 g., or a 98% yield, of white plates melting at 117-118°. One crystallization from methyl alcohol raised the melting point to 118-119°.

Anal. Calcd. for $C_{12}H_8NSCl$: N, 5.99. Found: N, 6.03.

2-γ-Diethylaminopropylamino-3-chlorodibenzothiophene.

A mixture of 7.0 g. (0.03 mole) of 2-amino-3-chlorodibenzothiophene and 9.3 g. (0.05 mole) of γ-diethylaminopropyl chloride hydrochloride was heated at 135-140°. After four hours, the reaction mixture was dissolved in water and treated as previously described under the preparation of 2-γ-diethylaminopropylaminodibenzothiophene (p. 64). The product distilled at 215-220° at a pressure of less than 0.1 mm. It was a yellow oil and weighed 5.5 g. corresponding to a yield of 53%.

Anal. Calcd. for $C_{19}H_{23}N_2SCl$: N, 8.08. Found: N, 7.97.

4-Aminodibenzothiophene.

Jacoby[45] has prepared 4-aminodibenzothiophene both by the Bücherer reaction (25% yield) and by amination of 4-bromodibenzothiophene (35% yield). It was found that the compound could be prepared more conveniently by reacting 4-lithiodibenzothiophene with α-methylhydroxylamine.

A solution of n-butyllithium, prepared from 137 g. (1.0 mole) of n-butyl bromide in 150 cc. of ether and 17.5 g. (2.5 gram atoms) of lithium metal in 500 cc. of ether, was added to 78 g. (0.424 mole) of dibenzothiophene. This solution was stirred and heated at reflux temperature for twenty hours. At the end of this time, an aliquot was withdrawn and titrated[46] to determine the approximate content of organometallic compounds. Since the solution was found to be approximately 0.64 molar in organolithium compounds, 10 g. (0.21 mole) of α-methylhydroxylamine in 60 cc. of ether was added slowly with constant stirring while the solution was cooled in an ice-salt bath. The solution became brown during the addition of the amine solution and a flocculent precipitate settled. The ice bath was removed and the mixture refluxed for one-half hour to make certain that the reaction was completed. The solution was cooled again in an ice bath and very carefully hydrolyzed by the very slow addition of 200 cc.

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[45] Gilman and Jacoby, J. Org. Chem., 3, 108 (1938).

[46] Haubein, Doctoral Dissertation, Iowa State College, (1942). See, also, J. Am. Chem. Soc., Sept. (1944).

of dilute hydrochloric acid, with vigorous stirring. The ether layer was separated and the aqueous solution extracted twice with 100 cc. portions of ether. The combined extracts were dried and then dry hydrogen chloride gas was passed in to precipitate the amine hydrochloride. When the solution was saturated with hydrogen chloride, the amine hydrochloride was filtered off and suspended in a liter of cold dilute ammonium hydroxide solution. The free amine was filtered and recrystallized from methyl alcohol. The yield of the pure 4-aminodibenzothiophene, melting at 110°, was 26 g. or 64% (based on the α-methylhydroxylamine). A mixed melting point with an authentic specimen of 4-aminodibenzothiophene showed no depression.

In addition there was recovered from the original ether solution 30 g. of dibenzothiophene. Apparently part of the 4-lithiodibenzothiophene reacts with the hydrogen of the α-methylhydroxylamine instead of the methoxyl group.

4-γ-Diethylaminopropylaminodibenzothiophene.

A mixture of 6.5 g. (0.032 mole) of 4-aminodibenzothiophene and 9.3 g. (0.05 mole) of γ-diethylaminopropyl chloride hydrochloride was heated under an atmosphere of nitrogen at 150-155°. After four hours, the reaction mixture was dissolved in water and treated as previously described under the preparation of 2-γ-diethylaminopropylaminodibenzothiophene (p. 64). The product distilled at 210-213° at a pressure of less than 0.1 mm.

It was a light yellow oil and weighed 7.5 g. corresponding to a yield of 73.5%.

Anal. Calcd. for $C_{19}H_{24}N_2S$: N, 9.00. Found: N, 9.12.

1-Bromo-4-γ-diethylaminopropylaminodibenzothiophene.

The necessary 1-bromo-4-aminodibenzothiophene was prepared essentially according to the direction of Jacoby[45]. Ten grams of 4-acetaminodibenzothiophene yielded 6 g. of 1-bromo-4-aminodibenzothiophene.

A mixture of 5.0 g. (0.018 mole) of 1-bromo-4-aminodibenzothiophene and 6.0 g. (0.0322 mole) of γ-diethylaminopropyl chloride hydrochloride was heated under an atmosphere of nitrogen at 145-150°. After three and one-half hours, the reaction mixture was dissolved in water and treated as previously described under the preparation of 2-γ-diethylaminopropylaminodibenzothiophene (p. 64). Five and four-tenths grams (76.7%) of yellow oil distilled over at 263-266°/0.3 mm.

Anal. Calcd. for $C_{19}H_{23}N_2SBr$: N, 7.16. Found: N, 7.23.

1-Nitro-4-methoxydibenzothiophene.

The necessary 4-methoxydibenzothiophene was prepared essentially according to the directions of Jacoby[45] by oxidizing the 4-lithiodibenzothiophene followed by methylation of the resulting 4-hydroxydibenzothiophene.

Twenty five grams (0.116 mole) of 4-methoxydibenzothiophene was dissolved in 400 cc. of glacial acetic acid and cooled to 15°. Twenty cubic centimeters of fuming nitric acid (sp. g., 1.49) was added with stirring over a period of ten minutes. The mixture was kept at 18-20° for ten minutes and filtered. The precipitate was washed with acetic acid and then with water. The dry product, melting at 159-161°, weighed 20 g. (a 66.6% yield). One crystallization from ethyl alcohol gave the pure product melting at 161-162°.

Anal. Calcd. for $C_{13}H_9O_3NS$: N, 5.45. Found: N, 5.58.

1-Amino-4-methoxydibenzothiophene.

A solution of 60 g. (0.267 mole) of hydrated stannous chloride in 70 cc. of concentrated hydrochloric acid was added to a suspension of 18.0 g. (0.071 mole) of 1-nitro-4-methoxydibenzothiophene (m. p., 159-161°) in 350 cc. of acetic acid and the mixture was heated in the water bath. After twenty minutes, a white precipitate separated out. Heating was continued for an additional 30 minutes. The solution was cooled and the precipitate filtered. The precipitate was treated with an excess of 25% sodium hydroxide solution, filtered, and the precipitate recrystallized from ethyl alcohol. The yield of the pure product, melting at 101-102°, was 12.7 g. or 81%.

Anal. Calcd. for $C_{13}H_{11}ONS$: N, 6.11. Found: N, 6.16.

In addition, one gram of a less soluble amino compound was

separated first from the ethyl alcohol. This product melted at 132-133°. By analogy with the nitration of 4-methoxydibenzofuran with fuming nitric acid (p. 58) at 18-20° which gives only 1-nitro-4-methoxydibenzofuran, it was assumed that the main product (m. p., 101-102°) was 1-amino-4-methoxydibenzothiophene and the smaller fraction (m. p., 132-133°) was 3-amino-4-methoxydibenzothiophene.

Anal. Calcd. for $C_{13}H_{11}ONS$: N, 6.11. Found: N, 6.21.

1-γ-Diethylaminopropylamino-4-methoxydibenzothiophene.

Five grams (0.022 mole) of 1-amino-4-methoxydibenzothiophene and 7.5 g. (0.04 mole) of γ-diethylaminopropyl chloride hydrochloride were heated to a temperature of 150-155° for four hours. The reaction mixture was dissolved in water and treated as previously described under the preparation of 2-γ-diethylaminopropylaminodibenzothiophene (p. 64). Three and seven-tenths grams (a yield of 49%) of yellow oil distilled over at 251-254°/0.15 mm.

Anal. Calcd. for $C_{20}H_{26}ON_2S$: N, 8.12. Found: N, 7.94.

FURTHER STUDIES ON THE BRIDGING OF THE 1- AND 9-POSITIONS OF DIBENZOFURAN

Introduction

The following investigation was undertaken with the hope of obtaining dibenzofuran derivatives with the 1- and 9-positions bridged. It is believed that such compounds will have greater promise as pharmaceuticals than the corresponding open type derivatives. However, while this work was still in progress, the need for antimalarials having a relatively simple basic structure became very acute, and the author directed his efforts in that direction.

The various attempts to bridge the 1,9-position in dibenzofuran have been very satisfactorily reviewed by Yeoman[47]. Since all attempts to form a six-membered ring through the 1,9-position in dibenzofuran have been unsuccessful, it seemed feasible to attempt the formation of an eight-membered ring in that position. Robinson and Mosettig[48] and also Parker[45] have cyclized γ-2-dibenzofurylbutyric acid to 1-keto-1,2,3,4-tetrahydro-β-brazan, and 1-keto-1,2,3,4-tetrahydro-γ-brazan. Thus cyclic-ketones were prepared from γ-(4-methoxy-1-dibenzofuryl)-butyric acid and γ-(4,6-dimethoxy-1-dibenzofuryl)butyric acid.

The γ-(4-methoxy-1-dibenzofuryl)butyric acid was cyclized

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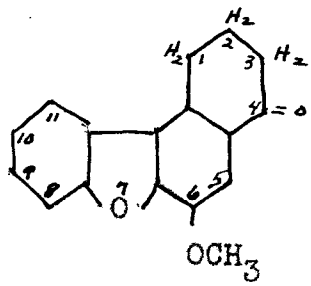
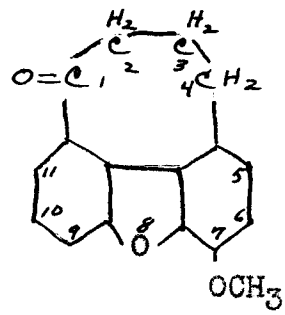
[47] Yeoman, Doctoral Dissertation, Iowa State College, (1944).

[48] Robinson and Mosettig, J. Am. Chem. Soc., 61, 2836 (1939).

with 88% sulfuric acid at room temperature to give a cyclic ketone in 76.6% yield. Only one product was isolated from this reaction. Depending upon the position involved in the ring-closure, there are two isomeric derivatives possible. If ring-closure has taken place at the 2-position, the product will be the 1,2,3,4-tetrahydro-6-methoxy-4-oxobenzo[b]naphtho[1,2-d]furan (IX), otherwise, it must be the 1,2,3,4-tetrahydro-7-methoxy-1-oxocyclo-octa[klm]dibenzofuran (X) in which closure has been affected through the 9-position. Oxidation of the ketone, followed by



IX



X

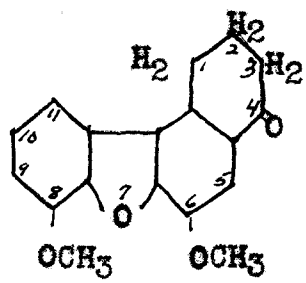
esterification yielded a dicarbomethoxy-4-methoxydibenzofuran which was not identical with the one obtained from 1,2-dibromo-4-methoxydibenzofuran through halogen-metal interconversion, carbonation, and esterification. The former compound was also obtained by Hogg[49] through oxidation of the cyclic-ketone, prepared from β-(4-methoxy-1-dibenzofuryl)propionic acid by dehydration, and esterification of the resulting di-acid. This is a strong indication that the former compound is 1,9-dicarbo-

[49] Hogg, Unpublished Studies.

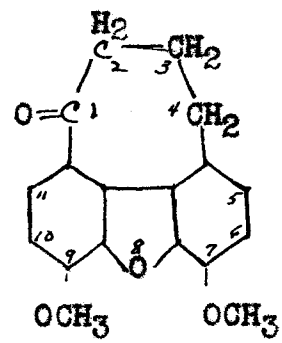
methoxy-4-methoxydibenzofuran and that the cyclization had involved the 9-position. This was expected since ring closure in the position meta (the 2-position) to the methoxyl group is unlikely because of the strong ortho - para directing influence of this group. However, it is possible that the 9-position is sterically hindered by the butyric acid group in the 1-position (see p. 93), and, if this is the case, the probability of a closure at the 2-position will be greater. Successful cyclization of γ-2-dibenzofurylbutyric acid[48] indicates that the position ortho to the butyric acid group is not sterically hindered. Unfortunately, the attempts to synthesize γ-(4-methoxy-2-bromo-1-dibenzofuryl)butyric acid were not successful. Successful cyclization of this compound would necessarily have involved the 9-position. This compound was to be debrominated and compared with the cyclic-ketone obtained from γ-(4-methoxy-1-dibenzofuryl)butyric acid.

The action of phosphorus pentachloride followed by anhydrous stannic chloride on γ-(4,6-dimethoxy-1-dibenzofuryl)butyric acid gave a cyclic-ketone in 67% yield. Again only one product was isolated. The two possible isomers are 1,2,3,4-tetrahydro-6,8-dimethoxy-4-oxobenzo[b]naphtho[1,2-d]furan (XI) and 1,2,3,4-tetrahydro-7,9-dimethoxy-1-oxocycloocta[klm]dibenzofuran (XII). In this case, the activity of the 2-position is still reduced by the methoxyl group in the 4-position but the 9-position is greatly activated by the methoxyl group in the 6-position. Barring the possibility of steric hindrance, the cyclization must have

involved the 9-position to give compound XII. It was hoped that oxidation of this compound would yield 4,6-dimethoxydibenzofuran-1,9-dicarboxylic acid which could also be synthesized from β-(1-bromo-4,6-dimethoxy-9-dibenzofuroyl)propionic acid* through oxidation to 1-bromo-4,6-dimethoxy-9-dibenzofurancarboxylic acid, replacement of the bromo group with a cyano group, and hydrolysis. Unfortunately, the small amount of acid obtained from 0.5 g. of the ketone could not be purified. Another attempt was not made because of lack of time and material.



XI



XII

*The structure of this compound is discussed on Page 17.

Experimental

β-(4-Methoxy-1-dibenzofuroyl)propionic acid.

The following procedure is based on the one used by Fieser and Hershberg[50] for the Friedel-Crafts reaction on succinic anhydride with phenol esters.

4-Methoxydibenzofuran, 99 g. (0.5 mole), and succinic anhydride, 55 g. (0.55 mole), were suspended in a mixture of 400 cc. of tetrachloroethane and 200 cc. of nitrobenzene contained in a three-necked flask fitted with a mechanical stirrer and immersed in an ice bath. With the temperature of the mixture held at 0-5°, 147 g. (1.1 moles) of powdered aluminum chloride was added in small portions over a period of an hour with vigorous stirring. Stirring was continued at this temperature for four hours and the reaction packed in ice overnight. The reaction was again stirred for eight hours at 0-5° and then hydrolyzed with ice and hydrochloric acid. The resulting mixture was subjected to steam distillation until a soft cake had formed in the flask. The aqueous layer was decanted from the residue and the cake washed by decantation. Fifty grams of sodium carbonate in 300 cc. of water was then added and the steam distillation continued until the remainder of the solvents had been carried over. The residue was filtered and extracted several times with hot sodium carbonate solution until all

[50] Fieser and Hershberg, J. Am. Chem. Soc., 58, 2314 (1936).

soluble material had been removed. The combined filtrates were acidified with dilute hydrochloric acid and the dried precipitate recrystallized from acetic acid to give 138 g. or a 92% yield of the purified compound melting at 224-225°.

Anal. Calcd. For $C_{17}H_{14}O_5$: C, 68.45; H, 4.69.

Found: C, 68.71; H, 4.98.

Oxidation of 1 g. of the above compound in 150 cc. of water containing 2 g. of sodium hydroxide with 3 g. of potassium permanganate gave a material which did not depress the melting point when mixed with an authentic specimen of 4-methoxy-1-dibenzofurancarboxylic acid[45].

γ-(4-Methoxy-1-dibenzofuryl)butyric acid.

The procedure of Martin[51] was used for this reduction. Fifty grams of mossy zinc was amalgamated by his method and placed in a round bottomed flask. Then 30 g. (0.101 mole) of β-(4-methoxy-1-dibenzofuroyl)propionic acid was added, with 40 cc. of water, 90 cc. of concentrated hydrochloric acid, 200 cc. of toluene, and 100 cc. of acetic acid. The mixture was brought to a boil and refluxed for 30 hours. At approximately 6-hour intervals, three 25 cc. portions of concentrated hydrochloric acid were added through the condenser. After refluxing was stopped, the toluene was removed by steam distillation and

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[51] Martin, ibid., 58, 1438 (1936).

the mixture allowed to cool. The cake was broken up, dried, and recrystallized from ethyl alcohol. The yield of the pure product, melting at 165°, was 23 g. or 81%. Recovered starting material weighed about 2 g.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.83; H, 5.63.

Found: C, 71.93; H, 5.81.

Cyclization of γ-(4-methoxy-1-dibenzofuryl)butyric acid.

Four grams (0.014 mole) of γ-(4-methoxy-1-dibenzofuryl)-butyric acid was stirred into 100 cc. of 88% sulfuric acid and the mixture allowed to stand at room temperature for fifteen minutes. The resulting deep red solution was poured on ice and the dilute acid decanted from the precipitate. The crude material was washed by decantation and warmed with 50 cc. of 10% sodium carbonate solution. The insoluble product was filtered and recrystallized from alcohol to give 2.8 g., or a 76.6% yield, of pure product melting at 165°. This is probably 1,2,3,4-tetrahydro-7-methoxy-1-oxocyclooctа[klm]dibenzofuran (X).

Anal. Calcd. for $C_{17}H_{14}O_3$: Mol. wt., 266; C, 76.70; H, 5.26.

Found: Mol. wt., 281; C, 76.86; H, 5.41.

Oxime of 1,2,3,4-tetrahydro-7-methoxy-1-oxocyclooctа[klm]dibenzofuran (X).

A solution of 1.0 g. (0.0037 mole) of 1,2,3,4-tetrahydro-7-methoxy-1-oxocyclooctа[klm]dibenzofuran in 50 cc. of

alcohol was refluxed five hours with 0.33 g. (0.0048 mole) of hydroxylamine hydrochloride and 1.0 cc. of 50% potassium hydroxide solution. The solution was poured into water and acidified with acetic acid. Crystallizing the precipitate from alcohol gave 0.8 g., or an 81% yield, of the pure oxime melting at 196-197°.

Anal. Calcd. for $C_{17}H_{15}O_3N$: N, 4.98. Found: N, 5.11.

Oxidation of 1,2,3,4-tetrahydro-7-methoxy-1-oxocycloocta[klm]-dibenzofuran (X).

Oxidation of one gram of 1,2,3,4-tetrahydro-7-methoxy-1-oxocycloocta[klm]dibenzofuran in 150 cc. of water containing 3 g. of sodium hydroxide and 500 g. of potassium permanganate gave 0.5 g. of base soluble product which could not be purified by crystallization.

An excess of diazomethane in ether, prepared from ethyl N-nitroso-N-methyl-carbamate by the method of V. Pechmann[52] was poured on the base soluble product. The reaction mixture was allowed to stand overnight, the ether was evaporated, and the residue was recrystallized from methyl alcohol. One-tenth of a gram of pure product, melting at 174-175°, was isolated. It is probably 1,9-dicarbomethoxy-4-methoxydibenzofuran.

Anal. Calcd. for $C_{17}H_{14}O_6$: CH_3O, 29.98. Found: CH_3O, 30.02.

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[52] Pechmann, Ber., 28, 855 (1895).

2-Bromo-4-hydroxydibenzofuran.

The necessary 2-bromo-4-dibenzofuryllithium was prepared according to the directions of Gilman and co-workers[53]. One-half mole of butyllithium, prepared from 137 g. (1.0 mole) of butyl bromide in 300 cc. of ether and 14 g. (1.0 g. atom) of lithium in 200 cc. of ether, was added to 247 g. (1.0 mole) of 2-bromodibenzofuran in 1.5 liters of benzene and the solution was refluxed for 10 hours. Then, in accordance with the procedure of Ivanoff, one-half mole of butylmagnesium bromide in 200 cc. of ether was added to improve the yield of oxidation product. The reaction was cooled below zero in an ice-salt mixture, and oxygen (bubbled through sulfuric acid and passed over soda lime) was swept over the surface of the well stirred solution at such a rate as to maintain the temperature below zero until a negative color test was obtained.

The lithium salt was hydrolyzed in a four-liter beaker containing ice and hydrochloric acid. The aqueous portion was extracted once with ether and discarded. The ether layers were combined and extracted with dilute sodium hydroxide solution. The alkaline solution was filtered, acidified, and cooled under the tap with shaking. The precipitate was filtered and recrystallized from benzene. The yield of 2-bromo-4-hydroxydibenzofuran, melting at 154-156°, was 27.5 g. or 21%.

Anal. Calcd. for $C_{12}H_7O_2Br$: Br, 30.41. Found: Br, 30.68.

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[53] Gilman, Cheney, and Willis, J. Am. Chem. Soc., 61, 951 (1939).

2-Bromo-4-methoxydibenzofuran.

To a stirred solution of 27 g. (0.102 mole) of 2-bromo-4-hydroxydibenzofuran in 300 cc. of water containing 5 g. of sodium hydroxide, was added dropwise 30 cc. (0.202 mole) of dimethyl sulfate. After all of the dimethyl sulfate was added, the mixture was refluxed for one-half hour. Then 10 g. of sodium hydroxide was added to destroy the unused ester and heating was continued for an additional thirty minutes. The reaction mixture was cooled and the precipitate filtered. One crystallization from ethyl alcohol gave colorless needles, m.p., 106-107°. The yield was 26.5 g. or 95%.

Anal. Calcd. for $C_{13}H_9O_2Br$: Br, 28.88. Found: Br, 28.92.

β-(4-Methoxy-2-bromo-1-dibenzofuroyl)propionic acid.

2-Bromo-4-methoxydibenzofuran, 28 g. (0.101 mole), and succinic anhydride, 11 g. (0.11 mole), were suspended in a mixture of 200 cc. of tetrachloroethane and 100 cc. of nitrobenzene contained in a three-necked flask fitted with a mechanical stirrer and immersed in an ice bath. With the temperature of the mixture held at 0-5°, 29 g. (0.22 mole) of powdered aluminum chloride was added in small portions over a period of one-half hour with vigorous stirring. Stirring was continued at this temperature for four hours and the flask containing the reaction mixture was packed in ice overnight. The reaction was again stirred for four hours at 0-5° and then hydrolyzed with ice and hydrochloric acid. The resulting

solution was subjected to steam distillation until a soft cake had been formed in the flask. The aqueous layer was decanted from the residue and the cake washed by decantation. Ten grams of sodium carbonate in 60 cc. of water was then added and the steam distillation continued until the remainder of the solvent had been carried over. The residue was filtered and extracted several times with sodium carbonate solution until all soluble material had been removed. The combined filtrates were acidified with dilute hydrochloric acid and the dried precipitate recrystallized from acetic acid to give 27 g., or a 71% yield, of the purified compound melting at 194-195°.

Anal. Calcd. for $C_{17}H_{13}O_5Br$: Br, 21.22. Found: Br, 21.36.

Four-tenths of a gram (0.0010 mole) of the above product was suspended in 40 cc. of absolute alcohol with 1 g. of palladium-carbonate catalyst and shaken with hydrogen under a gauge pressure of thirty-five pounds for thirty minutes at room temperature. The catalyst was filtered off and the filtrate diluted with water. The β-(4-methoxy-1-dibenzofuroyl)propionic acid, melting at 224-225°, precipitated in quantitative yield. When mixed with the authentic specimen of β-(4-methoxy-1-dibenzofuroyl)propionic acid (p. 79) no depression in melting point was observed.

Attempted preparation of γ-(4-methoxy-2-bromo-1-dibenzofuryl)-butyric acid.

Fifteen grams of β-(4-methoxy-2-bromo-1-dibenzofuroyl)-propionic acid was suspended in a mixture of 60 cc. of toluene, 10 cc. of acetic acid, 25 cc. of water and 60 cc. of concentrated hydrochloric acid, and refluxed for thirty-five hours with 40 g. of amalgamated zinc. Three additional 15 cc. portions of concentrated hydrochloric acid were added at approximately eight hour intervals. The toluene was separated from the aqueous layer and on cooling deposited 6 g. of compound melting at 156-158°. Crystallization from ethyl alcohol raised the melting point to 164-165°. A mixed melting point with an authentic specimen of γ-(4-methoxy-1-dibenzofuryl)butyric acid showed no depression. The residue from the evaporation of the alcohol gave a negative test for halogen or sodium fusion.

1,2-Dibromo-4-methoxydibenzofuran.

A solution of 2.75 g. (0.017 mole) of bromine in 17 cc. of acetic acid was added in several portions to a solution of 4.7 g. (0.017 mole) of 2-bromo-4-methoxydibenzofuran in 50 cc. of acetic acid at room temperature with shaking. Decolorization was immediate. After standing overnight the product was thrown out of solution by dilution with water and filtered. Crystallization from ethyl alcohol gave 5 g., or an 84% yield, of material melting at 127-128°.

Anal. Calcd. for $C_{13}H_8O_2Br_2$: Br, 44.94. Found: Br, 45.08.

The structure of the bromination product was not established but in all probability it is 1,2-dibromo-4-methoxydibenzofuran. This assumption is based on the fact that succinoylation of 2-bromo-4-methoxydibenzofuran involves the 1-position (p.92).

1,2-Dicarbomethoxy-4-methoxydibenzofuran.

To 4.4 g. (0.012 mole) of 1,2-dibromo-4-methoxydibenzofuran dissolved in 150 cc. of ether was added a solution of n-butyllithium, prepared from 1.4 g. of lithium and 6.3 cc. of n-butyl bromide in 60 cc. of ether. A milky-white precipitate began to form almost at once. The mixture was heated at reflux temperature for one hour and then carbonated by pouring on crushed solid carbon dioxide. After removal of the solvent by distillation, the residue was extracted with hot 5% potassium hydroxide solution. Acidification of the extraction liquid gave one gram (30.0%) of acid melting at 190-203°.

The above acid was dissolved in 50 cc. of methanol and refluxed for one hour while dry hydrogen chloride was passed into the solution. The product precipitated on cooling and was filtered. Three crystallizations from methanol gave the pure di-ester melting at 165-166°.

Anal. Calcd. for $C_{17}H_{14}O_6$: CH_3O, 29.98. Found: CH_3O, 30.26.

A mixed melting point with the di-ester obtained by esterification of the oxidation product of the cyclic-ketone was depressed to 148°.

γ-(4-Methoxy-3-nitro-1-dibenzofuryl)butyric acid.

A solution of 4 g. (0.012 mole) of γ-(4-methoxy-1-dibenzofuryl)butyric acid in 100 cc. of glacial acetic acid was heated on the steam bath to 40-45°, and 4 cc. of fuming nitric acid (sp. g., 1.50) was added with good stirring in two portions. The solution was stirred at this temperature for one hour and allowed to cool. The precipitated nitro-compound was filtered and recrystallized to yield 2 g. (a 43.5% yield) of pure product melting at 169-170°.

Anal. Calcd. for $C_{17}H_{15}O_6N$: N, 4.25. Found: N, 4.10.

Oxidation of 1 g. of the above compound in 200 cc. of water containing 2 g. of sodium hydroxide with 6 g. of potassium permanganate gave a material melting at 269-270°. (This is probably 4-hydroxy-3-nitro-1-dibenzofurancarboxylic acid). About 0.1-0.2 g. of this compound was mixed with an equal quantity of copper powder and 5 cc. of quinoline and heated in a test tube immersed in a metal bath. The bath temperature was kept at about 200° for one hour. The catalyst was filtered and the filtrate poured into dilute hydrochloric acid. The precipitate was filtered and recrystallized from ethanol. The product melted at 194-194.5° and a mixed melting point with an authentic specimen of 3-nitro-4-hydroxydibenzofuran[44] showed no depression, thus proving that the compound was γ-(4-methoxy-3-nitro-1-dibenzofuryl)butyric acid.

β-(4,6-Dimethoxy-1-dibenzofuroyl)propionic acid.

4,6-Dimethoxydibenzofuran, 11.5 g. (0.05 mole), and succinic anhydride, 5.5 g. (0.055 mole), were suspended in a mixture of 50 cc. of tetrachloroethane and 25 cc. of nitrobenzene contained in a three-necked flask fitted with a mechanical stirrer and immersed in an ice bath. With the temperature of the mixture held at 0-5°, 14.7 g. (0.11 mole) of powdered aluminum chloride was added in small portions over a period of fifteen minutes. Stirring was continued at this temperature for 24 hours. The solvent was removed with steam and the residue extracted with hot potassium hydroxide solution until all soluble material had been removed. The combined filtrates were acidified with dilute hydrochloric acid and the dried precipitate recrystallized from ethanol to give 16 g. or a 91% yield of the purified compound melting at 241-242°.

Anal. Calcd. for $C_{18}H_{16}O_6$: CH_3O, 18.90; neut. equiv. 328.

Found: CH_3O, 18.97; neut. equiv. 332.

Oxidation of 0.5 g. of this compound in 100 cc. of water containing 1 g. of sodium hydroxide with 2 g. of potassium permanganate gave a material (m.p., 297-298°) which did not depress the melting point when mixed with an authentic specimen of 4,6-dimethoxy-1-dibenzofurancarboxylic acid[49].

γ-(4,6-Dimethoxy-1-dibenzofuryl)butyric acid.

Ten grams (0.0305 mole) of β-(4,6-dimethoxy-1-dibenzofuroyl)propionic acid was suspended in a mixture of 200 cc. of toluene, 25 cc. of acetic acid, 70 cc. of water, and 150 cc. of hydrochloric acid, and refluxed for thirty-five hours with 50 g. of amalgamated zinc. Three additional 25 cc. portions of concentrated hydrochloric acid were added at approximately ten hour intervals. The toluene was separated and on cooling yielded 4 g. (a 42% yield) of γ-(4,6-dimethoxy-1-dibenzofuryl)butyric acid melting at 197-198°.

Anal. Calcd. for $C_{18}H_{18}O_5$: C, 68.79; H, 5.73.

Found: C, 68.87; H, 5.89.

Approximately four grams of starting material was recovered from the above reaction.

Cyclization of γ-(4,6-dimethoxy-1-dibenzofuryl)butyric acid.

To a suspension of 3.2 g. (0.0101 mole) of γ-(4,6-dimethoxy-1-dibenzofuryl)butyric acid in 100 cc. of dry benzene was added 3.0 g. (0.0126 mole) of phosphorus pentachloride, and the mixture was stirred at room temperature for fifteen minutes to give a clear yellow solution. The solution was cooled in an ice bath, and a solution of 12.5 g. (0.048 mole) of anhydrous stannic chloride in 50 cc. of benzene was added dropwise to the stirred solution over a period of fifteen minutes. The stirring was continued for forty-five minutes after the addition had been

completed. The dark red mixture was hydrolyzed by the dropwise addition of cold concentrated hydrochloric acid followed by water. The benzene solution was separated, washed with dilute sodium carbonate solution to remove acid, and evaporated to dryness to yield a yellow solid. This solid was recrystallized from ethanol to give 2.0 g. (67%) of colorless crystals. The ketone melted at 241-242°. This is probably 1,2,3,4-tetrahydro-7,9-dimethoxy-1-oxocyclooctaⁿ[klm]dibenzofuran (XII).

Anal. Calcd. for $C_{18}H_{16}O_3$: Mol. wt. 296; CH_3O 20.94.

Found: Mol. wt., 304; CH_3O, 20.98.

Oxidation of 1,2,3,4-tetrahydro-7,9-dimethoxy-1-oxocyclooctaⁿ[klm]dibenzofuran (XII).

Oxidation of 0.5 g. of 1,2,3,4-tetrahydro-7,9-dimethoxy-1-oxocyclooctaⁿ[klm]dibenzofuran in 200 cc. of water containing 3 g. of potassium hydroxide with 6 g. of potassium permanganate gave a very small amount of acid which resisted attempts at purification through crystallization.

Oxime of 1,2,3,4-tetrahydro-7,9-dimethoxy-1-oxocyclooctaⁿ[klm]-dibenzofuran (XII).

A solution of 0.5 g. (0.0017 mole) of 1,2,3,4-tetrahydro-7,9-dimethoxy-1-oxocyclooctaⁿ[klm]dibenzofuran in 100 cc. of alcohol was refluxed five hours with 0.2 g. of hydroxylamine hydrochloride and 0.5 cc. of 50% potassium hydroxide solution. The solution was poured into water and acidified with acetic acid. One

crystallization from ethyl alcohol gave 0.4 g. or a 74% yield of the pure oxime melting at 265°.

Anal. Calcd. for $C_{18}H_{17}O_4N$: N, 4.50. Found: N, 4.51.

β-(1-Bromo-4,6-dimethoxy-9-dibenzofuroyl)propionic acid.

Eight and five-tenths gram (0.064 mole) of powdered aluminum chloride was added to a mechanically stirred mixture of 9.2 g. (0.031 mole) of 1-bromo-4,6-dimethoxydibenzofuran, 3.2 g. (0.032 mole) of succinic anhydride, 150 cc. of tetrachloroethane, and 50 cc. of nitrobenzene cooled to 0°. The stirring was continued at this temperature for twenty hours. The solvent was removed with steam and the residue extracted with hot sodium carbonate solution until all soluble material had been removed. The combined filtrates were acidified with dilute hydrochloric acid and the dried precipitate recrystallized from ethyl alcohol to give 9 g. or a 71% yield of the purified compound melting at 188-189°.

Anal. Calcd. for $C_{18}H_{15}O_6Br$: Br, 19.65. Found: Br, 19.89.

Four-tenths of a gram (0.001 mole) of the above product was suspended in 50 cc. of absolute alcohol with 1.0 g. of palladium-calcium carbonate catalyst and shaken with hydrogen under a gauge pressure of 40 pounds for one-half hour at room temperature. The catalyst was filtered and the filtrate diluted with water. The acid, melting at 241-242°, precipitated in a quantitative yield. When mixed with an authentic specimen of

9-(4,6-dimethoxy-1-dibenzofuroyl)propionic acid, no depression in melting point was observed. This indicates that succinoylation of 1-bromo-4,6-dimethoxydibenzofuran involves the 9-position. However, Hogg[49] recently succinoylated 1-bromo-4,6-dimethoxydibenzofuran and after several crystallizations obtained a very small amount of compound melting at 187-189°. On the assumption that this was the same compound as the one obtained by the author (m.p., 188-189°) (a sample for mixed melting point was not available), he debrominated the compound catalytically to obtain a small amount of base soluble product melting at 155-157°. Apparently further study is necessary to establish with certainty whether the succinoylation involves the 9- or some other position. If the succinoylation actually involves the 9-position, it would be interesting in view of the recent developments which indicate that bromination of 1-bromo-4,6-dimethoxydibenzofuran does not involve the 9-position[49].

Since it had been definitely shown that monobromination of 4,6-dimethoxydibenzofuran gave 1-bromo-4,6-dimethoxydibenzofuran, it had been assumed that, because of the symmetry of the compound, bromination of the latter compound had involved the 9-position to give 1,9-dibromo-4,6-dimethoxydibenzofuran. Hogg[49] recently metalated 4,6-dimethoxydibenzofuran with butyllithium and reacted the metalated product with bromine to obtain a monobromodibenzofuran which was not identical with 1-bromo-4,6-dimethoxydibenzofuran. However, bromination of the former and the latter

compounds gave identical dibromo-4,6-dimethoxydibenzofuran. Consequently, the compound which was originally thought to be 1,9-dibromo-4,6-dimethoxydibenzofuran must be either 1,8- or 1,7-dibromo-4,6-dimethoxydibenzofuran. It has been suggested[54] that the entrance of a second bromine atom in the 9-position is sterically hindered by the bromine atom already in the 1-position. This theory can be put to test by brominating 1-nitro-4,6-dimethoxydibenzofuran and then replacing the nitro group with a hydrogen atom through reduction and diazotization of the resulting amine. Since a nitro group is relatively small compared with a bromine atom*, the bromination of the 1-nitro-4,6-dimethoxydibenzofuran should involve the 9-position and the final product should be identical with the known 1-bromo-4,6-dimethoxydibenzofuran. If this theory holds, the different positions involved in the succinoylation and bromination of the 1-bromo-4,6-dimethoxydibenzofuran can be explained. Groups smaller than the bromine atom or unsymmetrical groups with freedom of rotation can be substituted in the 9-position. Thus, the keto-acid group introduced by succinoylation can enter in the 9-position in such a way that only the carbon atom will be facing the bromine atom in the 1-position. This possibility will

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[54] Thirtle, Doctoral Dissertation, Iowa State College, (1943).

* Distances in Ångstrom units from the nucleus of the carbon atom of the benzene to center of nitro group and bromine atom are 1.92 and 2.11, respectively (Stanley and Adams, J. Am. Chem. Soc., 52, 1200 (1930).

be increased because the relatively negative oxygen atom of the ketone will be repelled by the negative bromine atom[55]. The carboxyethylene group need not be considered because of its great mobility due to a single bond linkage.

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55 Gilman, "Organic Chemistry", 2nd ed., John Wiley and Sons, New York (1943), p. 1855.

Note On Nomenclature

A letter of enquiry was sent to Dr. E. J. Crane, Editor of Chemical Abstracts, regarding the preferred names for the cyclic ketones obtained from the derivatives of γ-dibenzofurylbutyric acid. The following is a copy of the letter which he sent in reply.

June 28, 1944

Mr. Souren Avakian,
2711 Lincoln Way,
Ames, Iowa

Dear Mr. Avakian:

I am writing in answer to your letter of June 23 after consulting with Dr. Leonard T. Capell of this office, who specializes in the organic side of our work.

The ring system of compound I[56] has been named benzo/b/naphtho/1,2-d/furan. It has been so called in our indexes (see index for Volume 34). Compound I can be named 2,3-dihydro-6-methoxybenzo/b/-naphtho/1,2-d/furan-4(1)-one. This is named as a 2,3-dihydroderivative because the other hydrogens are represented in the -4(1)-one part of the name; i.e., in order to have a benzo/b/naphtho/1,2-d/furan-4(1)-one, there

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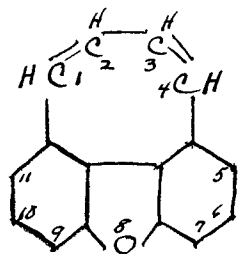
[56] Compound IX. This thesis, p.76.

must be an extra H atom present and the position of this extra H atom is shown by the (1) following the -4-. Named as an oxo derivative, the name would be 1,2,3,4-tetrahydro-6-methoxy-4-oxobenzo/b/naphtho/1,2-d/furan.

The compound II[57] represents a new ring system.



This is the form which is named and it is called cyclo-octa/klm/dibenzofuran. The klm represents the sides of the dibenzofuran which are a part of the cyclooctane ring.

The compound II, named with the ketone function in the parent name, is called 3,4-dihydro-7-methoxycyclooocta/klm/dibenzofuran-1(2)-one. It can also be called 1,2,3,4-tetrahydro-7-methoxy-1-oxocyclo-octa/klm/dibenzofuran.

Sincerely yours,

E. J. Crane

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[57] Compound X. This thesis, p. 76.

SUMMARY

1. It has been shown that amination of 4,6-diiododibenzofuran does not proceed normally to give 4,6-dibenzofuran.
2. A series of dibenzofuran derivatives containing the γ-diethylaminopropylamino side chain has been prepared.
3. A series of dibenzothiophene derivatives containing the γ-diethylaminopropylamino side chain has been prepared.
4. The results of the biological tests made on the above two series of compounds are given. None of the derivatives prepared in this investigation showed any definite antimalarial activity.
5. 1- γ-(4-methoxydibenzofuryl)butyric acid and 1-γ-(4,6-dimethoxydibenzofuryl)butyric acid have been cyclized successfully.