

1936

Dibenzofuran and phenothiazine derivatives

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DIBENZOFURAN AND PHENOTHIAZINE DERIVATIVES

BY

Paul Raymond VanEss

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A Thesis Submitted to the Graduate Faculty
for the degree of

DOCTOR OF PHILOSOPHY

Major Subject Organic Chemistry

Approved

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INTRODUCTION

The purpose for which experimental work with dibenzofuran derivatives was undertaken in this laboratory, and a historical development of the field have been set forth fully by W. H. Kirkpatrick (1).

Bromination studies of 2- and 3-acetaminodibenzofurans already having been completed in this laboratory, the writer was allotted the task of investigating the bromination reaction of 4-acetaminodibenzofuran and, in addition, 2-, 3-, and 4-hydroxy-dibenzofurans.

Bromination of 2-diacetamino- or 2-acetaminodibenzofuran occurs in the 3-position to give 2-acetamino-3-bromodibenzofuran, while 3-acetaminodibenzofuran brominates in the 2-position, yielding 2-bromo-3-acetaminodibenzofuran. The structure of these derivatives was established by conversion of each to the 2,3-diamine, whose ortho configuration was proven by formation of a quinoxaline derivative. Nitration of 2-acetamino- and 3-acetaminodibenzofurans follows bromination (2).

Shortly after the writer had undertaken bromination studies of the hydroxydibenzofurans, and simultaneously with publication of a paper on nuclear substitutions of dibenzofuran by Gilman and co-workers (2), there appeared an article by Tatematsu and

(1) Kirkpatrick, W.H., Doctoral Dissertation, Iowa State College, 1935.

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

Kubota (3) reporting the bromination of 3-hydroxydibenzofuran. They obtained 2-bromo-3-hydroxydibenzofuran and proved its structure by conversion from 2-bromo-3-aminodibenzofuran which, in turn, was synthesized and established independently in a similar manner to that employed by Gilman and co-workers (2).

(3) Tatematsu and Kubota, Bull. Chem. Soc. Japan, 9, 448 (1934).

DISCUSSION OF RESULTS

Bromination of 2-hydroxydibenzofuran gave predominantly a colorless crystalline monobromo derivative melting sharply at 123-123.5°. Treatment of this compound with dimethyl sulfate furnished a methoxy derivative melting at 117-118°.

Bromination of 2-hydroxydibenzofuran might be expected to take place in the 8-position, according to analogy with bromination of 2-bromodibenzofuran (4), or in the 1- or 3-position in consideration of the strong ortho and para orienting influence of the hydroxyl group. Experiments were undertaken to confirm or eliminate these possibilities.

Authentic 2-methoxy-8-bromodibenzofuran, prepared by a reliable ring closure method employed in the synthesis of similar derivatives (4), was found to melt at 92.5° and to be dissimilar from the 117-118° melting bromo-2-methoxydibenzofuran.

The next step in the proof of structure was the preparation of 2-hydroxy-3-bromodibenzofuran by conversion from the authentic 2-amino-3-bromodibenzofuran of Gilman and co-workers (2). 2-Hydroxy-3-bromodibenzofuran was found to melt at 143-144°, obviously dissimilar from the 123-123.5° melting isomer. Methylation of the 143-144° melting compound yielded 2-methoxy-3-bromodibenzofuran melting at 172°, which was found to be identical with the chief product from bromination of

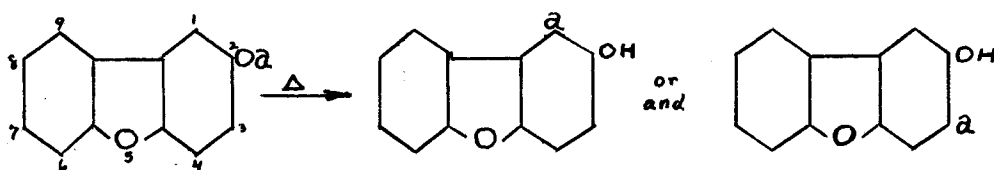
(4) McCombie, Macmillan, and Scarborough, J. Chem. Soc., 529 (1931).

2-methoxydibenzofuran. Since it was shown that the bromine atom had not entered the 3- or 8-position on bromination of 2-hydroxydibenzofuran, the only logical position left to consider was the 1-position. Proof of structure by ring closure methods was out of the question because no unambiguous synthesis was available.

The problem was finally solved by utilization of the Claisen allyl ether rearrangement (5a,b,c,6). Claisen has shown that when allylphenyl ether is heated, rearrangement occurs whereby the allyl group migrates to the ortho carbon atom of the nucleus to give o-allylphenol. If one of the ortho positions is occupied by a substituent group, the allyl group will always rearrange to the other ortho position; and if both ortho positions are blocked by substituent groups, the allyl group will migrate to the para-position. This is known as Claisen's rule (5d), and is supported by a good deal of experimental work by Claisen himself, and others.

Thus, according to this rule, the allyl group in 2-allyloxydibenzofuran, on heating, could rearrange only to the 1- or 3-position, or both (7).

- (5) (a) Claisen, Ber., 45, 3159 (1912); (b) Claisen and Eisleb, Ann., 401, 21 (1913); (c) Claisen, Eisleb, and Kramers, Ann., 418, 69 (1919); (d) Claisen and Eisleb, Ann., 401, 23 (1913).
- (6) An excellent summary of published work on the allyl ether rearrangement is found in C.D. Hurd's "Pyrolysis of Carbon Compounds", Chemical Catalog Co., 1929, pp. 214-228.
- (7) For the sake of convenience, the allyl group is denoted by a.



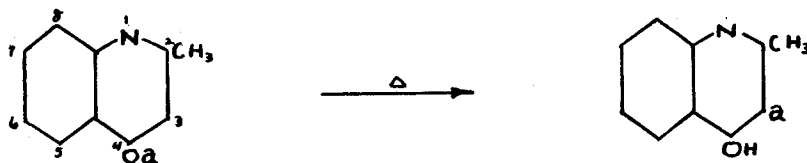
Most of the experimental work in support of Claisen's rule has been carried out with benzene derivatives. Can the assumption then be made that Claisen's rule holds for other aromatic nuclei, and for dibenzofuran in particular? Have any exceptions to this rule ever been reported?

Examining those few cases wherein the Claisen rearrangement has been carried out with allyl aryl ethers other than phenyl, we find that 2-allyloxynaphthalene gives a quantitative yield of 1-allyl-2-hydroxynaphthalene (5b); while 1-allyloxynaphthalene rearranges to 1-hydroxy-2-allylnaphthalene. However, 1-allyl-2-allyloxynaphthalene is stable when heated (5a). *p*-Allyloxydiphenyl also undergoes ortho rearrangement (8). 4-Allyloxy-1,2-naphthoquinone and 2-allyloxy-1,4-naphthoquinone both rearrange to 2-allyl-3-hydroxy-1,4-naphthoquinone (9).

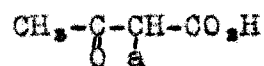
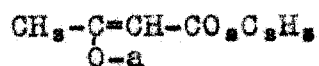
A most interesting and illuminating rearrangement is that of 4-allyloxyquinaldine (10). Anisole does not undergo any rearrangement on heating, but 4-methoxyquinaldine does, the methyl group migrating to the nitrogen atom (11). Similarly with 4-allyloxyquinaldine, it might be expected that the allyl group

- (8) Gilman and Kirby, *J. Am. Chem. Soc.*, **48**, 2191 (1926).
 (9) Fieser, *J. Am. Chem. Soc.*, **48**, 3205 (1926); *ibid.*, **49**, 857 (1927).
 (10) Mander-Jones and Trikojus, *J. Am. Chem. Soc.*, **54**, 2570 (1932).
 (11) Conrad and Limpach, *Ber.*, **20**, 956 (1887).

also would migrate to nitrogen. Such, however, is not the case, for rearrangement proceeds in accordance with Claisen's rule to give 3-allyl-4-hydroxyquinoline whose structure was proven by synthesis from α -allyl- β -hydroxy-phenylaminocrotonic ester.



For ortho rearrangement of allyl ethers, an α, β -unsaturated system is necessary (6), $\begin{matrix} \text{O}-a \\ | \\ -\text{C}=\text{CH}- \end{matrix}$, for Claisen has shown that allylcyclohexyl ether does not rearrange on heating in a sealed tube for several hours at 210° (5c). If this α, β -unsaturated system is a sufficient as well as necessary condition for ortho rearrangement, then the allyl alkyl as well as allyl aryl ethers should undergo this change. Such has been found to be the case with the purely aliphatic O -allylacetoacetic ester (5a).

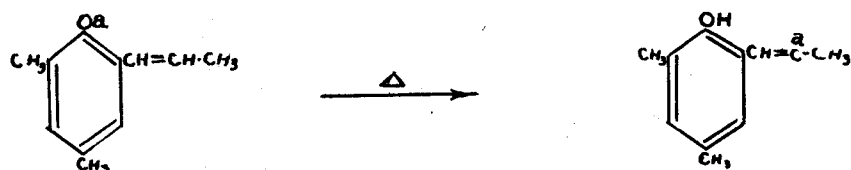


Para rearrangement involves a 1,4-conjugated system:



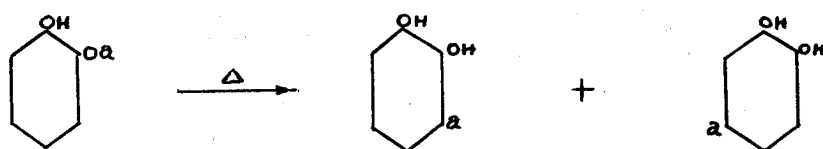
If the necessary and sufficient conditions for para rearrangement are fulfilled by this system, then it should be possible with proper blocking groups present to obtain a migration of the allyl group to an appropriate side chain as vinyl or propenyl. Such a migration was demonstrated by Claisen (12) in the (12) Claisen, Ann., 449, 84 (1926).

following transformation:



Since 2-allyloxydibenzofuran in common with other allyl aryl ethers possesses an α,β -unsaturated system, it may reasonably be assumed that its rearrangement will follow Claisen's rule.

No exceptions to Claisen's rule when both ortho positions are open have ever been noted. Only one exception, and a partial one at that, has ever been reported when one of the ortho positions contains a substituent group. Kawai (13) pyrolyzed the monoallyl ether of catechol, and obtained a mixture of 3-allyl- and 4-allylcatechol. He was not able to separate the two isomers but proved their existence by methylation, oxidation, and separation of the two resulting known acids.



Perkin and Trikojus (14) repeated this work and succeeded in separating the two isomers, the ratio of ortho to para isomer being 5:4. According to Claisen's rule, no para rearrangement

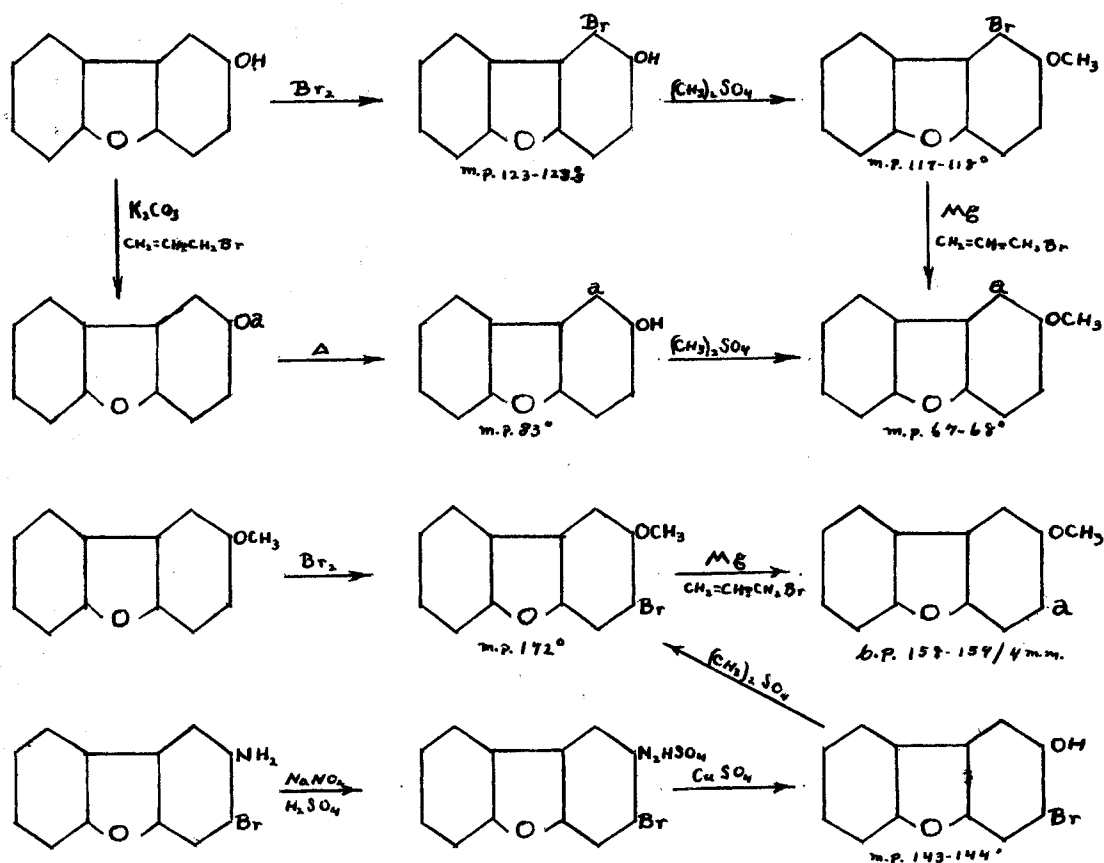
(13) Kawai, Sci. Papers Inst. Phys. Chem. Res. (Tokyo), **3**, 263 (1926).

(14) Perkin and Trikojus, J. Chem. Soc., 1663 (1927).

should have occurred unless both ortho positions were blocked. This exception does not militate against the applicability of Claisen's rule to the rearrangement of 2-allyloxydibenzofuran as there is no para position open, that is, no δ -hydrogen in the 1,4-conjugated system is available for interchange.

Accordingly, when 2-allyloxydibenzofuran was heated to 220-230°, an exothermic reaction occurred. The crude alkali soluble product, recrystallized from petroleum ether, yielded a colorless definitely crystalline ortho-allyl-2-hydroxydibenzofuran melting sharply at 83°. Treatment of this phenol with dimethyl sulfate yielded ortho-allyl-2-methoxydibenzofuran melting at 67-68° and which was found to be identical with the allyl-2-methoxydibenzofuran prepared from the 117-118° melting bromo-2-methoxydibenzofuran by reaction of its Grignard reagent with allyl bromide. Authentic 2-methoxy-3-allyldibenzofuran was also prepared by reaction of the Grignard reagent of 2-methoxy-3-bromodibenzofuran with allyl bromide and found to be a liquid, thus dissimilar from the 67-68° melting methylated Claisen rearrangement derivative. Since the allyl group in the 67-68° melting ortho-allyl-2-methoxydibenzofuran is shown to be not in the 3-position, it must, therefore, be in the 1-position. From the sequence of reactions described, it follows that the chief bromination product of 2-hydroxydibenzofuran is 1-bromo-2-hydroxydibenzofuran.

Reactions Involved in Proof of Structure of 1-Bromo-2-hydroxydi-benzofuran.



Coupling of benzenediazonium chloride with 2-hydroxydibenzofuran in alkaline solution was found to take place in the 1-position also, yielding 1-benzeneazo-2-hydroxydibenzofuran (15). This coupling was established by reductive cleavage of the azo compound to an amino-phenol which was converted by a modified Gattermann-Sandmeyer reaction to 1-bromo-2-hydroxydibenzofuran.

While bromination of 2-hydroxydibenzofuran gives as chief product 1-bromo-2-hydroxydibenzofuran, some of the 3-bromo (15) VanEss, M.W., Doctoral Dissertation, Iowa State College, 1936.

isomer is also formed. The residue obtained from the mother liquor was repeatedly recrystallized in vain to obtain the isomeric 2-hydroxy-3-bromodibenzofuran, but methylation of the residue and purification by repeated recrystallization gave a small amount of the 172° melting 2-methoxy-3-bromodibenzofuran. Also, some of the 1-bromo-2-methoxy isomer was obtained from the mother liquor of the bromination of 2-methoxydibenzofuran.

Bromination of 4-hydroxydibenzofuran yielded a monobrominated derivative melting at 151.5-152° and whose methylated derivative melted at 97-97.5°. P. T. Parker, in this laboratory, found that bromination of 4-methoxydibenzofuran occurred smoothly to give a good yield of a bromo-4-methoxydibenzofuran melting at 97-98°, which was found to be identical with the above methylated derivative of bromo-4-hydroxydibenzofuran. 4-Acetaminodibenzofuran on bromination and subsequent hydrolysis yielded a bromo-4-aminodibenzofuran melting at 119-120°. Conversion of this bromo-4-amine to the 151.5-152° melting bromo-4-hydroxydibenzofuran established the fact that the same position was involved in bromination of 4-acetamino- and 4-hydroxydibenzofurans.

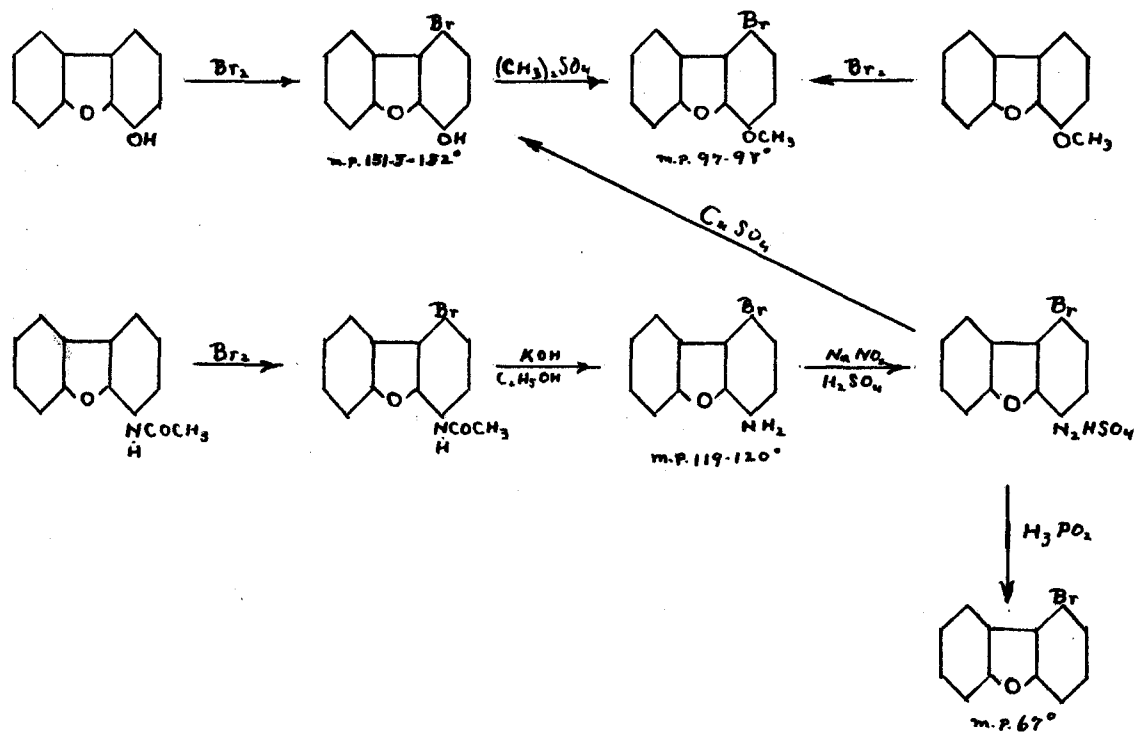
Theoretically, the most probable positions to be involved in substitution reactions of 4-hydroxydibenzofuran are the 1- and 3-positions on the basis of the strong ortho and para directing influence of the hydroxyl group.

Diazotation of the 119-120° melting bromo-4-aminodibenzofuran followed by the removal of the diazonium group with hypophosphorous acid gave a crystalline bromodibenzofuran melting

sharply at 67°. This compound was not identical with the 2-, 3-, or 4-bromodibenzofurans which had been previously established. That the dibenzofuran nucleus was intact after the series of transformations incidental to its preparation was established by dehalogenation and isolation of dibenzofuran.

By the method of exclusion, therefore, the 67° melting compound can be only 1-bromodibenzofuran; this was also converted to the 1-hydroxy-, 1-amino-, 1-acetamino-, 1-carboxy-, and 1-carbomethoxydibenzofurans; in each case the 1-derivative was found to differ from the corresponding 2-, 3-, and 4-substituted compounds, as will be seen in the table on page 18.

Reactions Involved in the Proof of Structure of Bromination
Products of 4-Acetamino-, 4-Hydroxy-, and 4-Methoxydibenzofurans.



Melting Points of Monosubstituted Dibenzofurans

	Br	OH	NH ₂	NHCOCH ₃	COOH	CO ₂ CH ₃
1-	67°	140-140.5°	74°	205°	232-233°	63°
2-	110° (a)	134° (b)	127-128° (c)	162-163° (c)	249° (d)	73-74° (d)
3-	120° (a)	138-138.5° (e)	101° (d)	178° (f)	271.5-272° (g)	138.5° (g)
4-	72° (h)	102° (i)	84.5-85.5° (j)	172.5° (j)	209-210° (k)	93-94° (l)

- (a) McCombie, Macmillan, and Scarborough, J. Chem. Soc., 529 (1931).
 (b) Gilman, Bywater, and Parker, J. Am. Chem. Soc., 57, 885 (1935).
 (c) Bywater, W.G., Doctoral Dissertation, Iowa State College, 1934.
 (d) Baillie, J.C., Unpublished work, Iowa State College, 1936.
 (e) Tsuzuki, Bull. Chem. Soc. Japan, 2, 79 (1927).
 (f) Borsche and Schacke, Ber., 56, 2498 (1923).
 (g) Gilman, Smith, and Cheney, J. Am. Chem. Soc., 57, 2095 (1935).
 (h) Prepared in this laboratory by George Brown by the reaction of 4-dibenzofuryl-lithium with bromine vapor in ether solution.
 (i) Gilman and Young, J. Am. Chem. Soc., 57, 1121 (1935).
 (j) Kirkpatrick and Parker, J. Am. Chem. Soc., 57, 1123 (1935).
 (k) Kruber, Ber., 55, 1382 (1932).
 (l) Hayes, D.M., Unpublished Master's Thesis, Iowa State College, 1934.

From the isolation of 1-bromodibenzofuran, the conclusion can be drawn that the bromination of 4-acetaminodibenzofuran, and consequently that of 4-hydroxy- and 4-methoxydibenzofuran, involves the 1- or 9-position. Consideration of the strong ortho- and para-directing influence of acetamino, hydroxyl, and methoxy groups leads one further to conclude that 1- or homo-substitution is extremely probable and that 9- or hetero-substitution is but a remote possibility.

In order to adduce experimental evidence of homosubstitution, an unsuccessful attempt was made to prepare 1,4-dimethoxydibenzofuran by ring closure of 2-amino-2',5'-dimethoxydiphenyl ether. This failure was not unexpected, as others have experienced negative results in attempting to prepare 4-substituted dibenzofurans by the diphenyl ether ring closure method. McCombie, and co-workers (4) were not able to prepare 4-chlorodibenzofuran from 2-amino-2'-chlorodiphenyl ether. P.T. Parker, in this laboratory, obtained only phenolic products in an attempted ring closure of 2-methoxy-2'-amino-4'-bromodiphenyl ether.

M.W. VanEss (15), in this laboratory, found that benzene-diazonium chloride couples with the sodium salt of 4-hydroxydibenzofuran in the same position taken by bromine in substitution. This fact was established by conversion of the benzeneazo compound to the 151.5-152° melting 1-bromo-4-hydroxydibenzofuran by reductive cleavage followed by a modified Gattermann-Sandmeyer reaction.

A.L. Jacoby and J. Swislowsky, in this laboratory, studied the nitration of 4-substituted dibenzofuran derivatives and found that 4-hydroxy- and 4-acetaminodibenzofurans when treated with fuming nitric acid in acetic anhydride at low temperatures yield respectively, 3-nitro-4-hydroxydibenzofuran, melting at 193°, and 3-nitro-4-acetaminodibenzofuran, melting at 238°. Proof of structure of these compounds rested on conversion of the 3-nitro-4-amine to a quinoxaline forming ortho diamine, and conversion of the 3-nitro-4-amine to the 3-nitro-4-hydroxydibenzofuran. On the other hand, they found that under the same conditions 4-methoxydibenzofuran yields principally 1-nitro-4-methoxydibenzofuran melting at 154.5-155°, and whose structure was determined by catalytic reduction to the 1-amino-4-methoxydibenzofuran, identical with the amination product of the writer's 1-bromo-4-methoxydibenzofuran. They also found that nitration of 4-acetaminodibenzofuran with fuming nitric acid in glacial acetic acid at 60° resulted in the isomeric 1-nitro-4-acetaminodibenzofuran melting at 216°. The orientation of this derivative was established by conversion to the corresponding, 1,4-dimonoacetaminodibenzofuran which was identical with the acetylation product of the 1,4-diamine obtained by amination of the 1-bromo-4-aminodibenzofuran. Deamination of 1-nitro-4-aminodibenzofuran yielded 1-nitrodibenzofuran melting at 120-121°.

P.T. Parker, in this laboratory, found that Friedel-Crafts acetylation of 4-methoxydibenzofuran takes place in the 1-position to give 1-acetyl-4-methoxydibenzofuran. This compound was

oxidized to 1-carboxy-4-methoxydibenzofuran melting at 279-280°, and found to be identical with the acid obtained by carbonation of the Grignard reagent of the writer's 1-bromo-4-methoxydibenzofuran.

Likewise, L.C. Cheney, in this laboratory, obtained 1-chloroacetyl-4-methoxydibenzofuran by the Friedel-Crafts reaction of chloroacetyl chloride with 4-methoxydibenzofuran. This compound was also oxidized to the 279-280° melting 1-carboxy-4-methoxydibenzofuran. An attempt to obtain intramolecular coupling of the 1-chloroacetyl group in the 9-position to prepare a phenanthroline derivative was unsuccessful.

Nitration of 1-carbomethoxydibenzofuran yielded a mononitro-ester melting at 216°. The nitro-acid obtained by hydrolysis was decarboxylated by heating with quinoline and copper. Steam distillation of the acidified reaction mixture yielded 3-nitrodibenzofuran, found identical with an authentic specimen. Thus, 3- or 7-substitution must have occurred.

Dibenzofuran nitrates normally and smoothly in the 3-position (16). The relative ease of nitration of 1-carbomethoxydibenzofuran, accomplished by concentrated nitric acid at room temperature, indicates that 7- or heterosubstitution is the more likely, for introduction of a nitro group meta to a carboxyl group is, in general, of a relatively greater degree of difficulty. This assumption is supported by the verified hypothesis (15) that dibenzofurans, monosubstituted with meta-directing groups, undergo further substitution in hetero fashion.

(16) Borsche and Bothe, Ber., 41, 1990 (1908).

EXPERIMENTAL

Preparation of 2-Hydroxydibenzofuran.

The preparation of 2-hydroxydibenzofuran in 36.7% yield by oxidation of 2-dibenzofurylmagnesium bromide in the presence of n-butylmagnesium bromide was accomplished by W.G. Bywater (17). This procedure was followed by the writer, but found to be not too satisfactory because of low yields and time and labor involved.

In 1935, a German patent appeared (18) describing the preparation of 2-hydroxydibenzofuran by treatment of 2-bromodibenzofuran with dilute alkalis or alkaline earths in an autoclave at high temperatures. As an example, "50 g. of 2-bromodibenzofuran with 250 g. of 16% sodium hydroxide was heated in an autoclave at 250° for eight hours." Typical of patent descriptions, the catalyst used was not mentioned. Such a catalyst was found necessary, for when 2-bromodibenzofuran was treated under the conditions specified in the patent, no phenol was obtained.

After several trial runs, copper sulfate and metallic copper were found to be effective catalysts. In a typical run, 100 g. (0.405 mole) of 2-bromodibenzofuran, 85 g. of sodium hydroxide dissolved in 100 cc. of water, 30 g. of copper sulfate dissolved in 150 cc. of water, 100 g. of copper turnings, and 10 g. of

(17) Gilman, Bywater, and Parker, J. Am. Chem. Soc., 57, 885 (1935).

(18) I.G. Farbenind., A.G., German Patent 606,350 ∩C.A., 29, 1434 (1935) ∩.

copper bronze were placed in a steel bomb (19) of about one-liter capacity and heated for twelve hours at 240°. On cooling, the contents were transferred to a two-liter Erlenmeyer flask, diluted with a liter of water, and brought to boiling to insure complete solution of the sodium salt. The solution was filtered, cooled, and acidified with hydrochloric acid; whereupon the phenol came down as a brown solid melting at 117-120°. The crude yield was 49 g. (0.266 mole) or 64%. In other runs, the crude yield varied from 56-75%. Distillation was found to be the most convenient method of purification; 100 g. of the crude phenol was distilled at 175-180°/ 5mm. to give 78 g. of pure white material melting at 125-130°. One recrystallization from water sufficed to bring the melting point to 134°.

Bromination of 2-Hydroxydibenzofuran.

To a solution of 18.4 g. (0.10 mole) of 2-hydroxydibenzofuran dissolved in 300 cc. of glacial acetic acid, 100 cc. of a molar solution of bromine in glacial acetic acid was added dropwise at room temperature with shaking. The bromine was taken up rapidly. After standing one hour, the solution was diluted with water to one liter, allowed to settle, and filtered. The crude bromination product, 23.4 g., melting at 113-118° was dissolved in 200 cc. of hot alcohol, refluxed with norite, and

(19) The writer wishes to thank Dr. F.E. Brown for the use of the steel bomb and assistance in its operation.

diluted with 200 cc. of hot water. On cooling, 19.05 g. of a white crystalline substance melting at 117-120° was obtained. Further recrystallization from a mixture of 180 cc. of benzene and 90 cc. of petroleum ether (b.p. 60-68°) gave 11.4 g. or a 43% yield of product melting at 123-123.5°. This melting point could not be improved by further recrystallization.

Analysis showed the substance to be a monobrominated derivative later proven to be 1-bromo-2-hydroxydibenzofuran. No color was developed on adding dilute ferric chloride to an alcohol solution of this phenol.

Anal. Calcd. for $C_{12}H_9O_2Br$: Br, 30.39. Found: Br, 30.74 and 30.58.

Methylation of 1-Bromo-2-hydroxydibenzofuran.

A solution of 5.26 g. (0.02 mole) of the above 1-bromo-2-hydroxydibenzofuran in 200 cc. of 10% sodium hydroxide was shaken with an excess of dimethyl sulfate added in three portions, then allowed to stand on a water bath for thirty minutes. The solid product, 3.88 g., a 76% yield, melted at 117-118°; this was recrystallized from alcohol to give a white crystalline substance still melting at 117-118°. Another recrystallization from benzene and petroleum ether (b.p. 60-68°) did not raise the melting point.

Anal. Calcd. for $C_{13}H_9O_2Br$: Br., 28.85. Found: Br, 29.12 and 29.35.

Preparation of 2-Methoxydibenzofuran.

A solution of 14.6^{*} g. (0.08 mole) of 2-hydroxydibenzofuran in dilute alkali (3.3 g. of sodium hydroxide in 200 cc. of water) was treated with 9 cc. of dimethyl sulfate. After shaking vigorously, an additional gram of sodium hydroxide was added and the reaction mixture allowed to stand on a water bath for one hour. On cooling, the product was extracted with ether, dried over anhydrous sodium sulfate, and distilled. Ten and one-tenth grams of the methyl-ether distilling at 164-165°/ 6 mm. was obtained. On standing in the ice box, the liquid product solidified in prisms melting at 45°. Recrystallization from petroleum ether (b.p. 60-68°) raised the melting point to 46-47°.

Anal. Calcd. for $C_{13}H_{10}O_2$: C, 78.76; H, 5.09. Found: C, 79.18; H, 5.15.

Bromination of 2-Methoxydibenzofuran.

Ten grams (0.05 mole) of 2-methoxydibenzofuran was dissolved in 50 cc. glacial acetic acid; to this was added with stirring 8 g. (0.05 mole) of bromine dissolved in 50 cc. of glacial acetic acid. After standing one hour, the bromination product was thrown out by diluting with water and filtered. The crude product, 14.7 g., melting at 113-162° was extracted with 100 cc. of boiling alcohol, filtered hot, and the residue extracted with another portion of hot alcohol and filtered. The residue, 4.4 g. melting at 168-171° was recrystallized from 30 cc. of benzene

to give 3.6 g. of white needles melting at 172°. On cooling, the second 100 cc. portion of alcohol yielded an additional gram of product melting at 171-172°. The total purified yield of monobrominated derivative was 4.6 g., or 53%. This derivative is shown later to be 3-bromo-2-methoxydibenzofuran.

Anal. Calcd. for $C_{12}H_9O_2Br$: Br, 28.85. Found: Br, 28.94 and 29.05.

On cooling, the first 100 cc. of alcohol used in extraction deposited 5.9 g. of brownish crystals melting at 100-140°. Further recrystallization from 200 cc. of 80% alcohol gave 5 g. of white crystals melting at 100-115°. The melting point was raised only to 107-150° by recrystallization from 40 cc. of a 1:1 mixture of benzene and petroleum ether (b.p. 60-68°). On slowly evaporating the benzene-petroleum ether filtrate, two different kinds of crystals were deposited, large prisms and small needles. Several of the large prisms were separated mechanically and found to melt at 117-118° and to be identical with 1-bromo-2-methoxydibenzofuran.

Preparation of 2-Hydroxy-3-bromodibenzofuran.

W.G. Bywater (2) prepared 2-acetamino-3-bromodibenzofuran by bromination of 2-diacetaminodibenzofuran. It was found that the more conveniently prepared 2-acetaminodibenzofuran could also be used.

2-Aminodibenzofuran was prepared by high temperature and pressure amination of the corresponding bromo-compound in

accordance with Bywater's directions (2). 2-Acetaminodibenzofuran was prepared by treatment of the amine with acetic anhydride in benzene solution (20).

Bromination of 2-acetaminodibenzofuran was effected by adding 100 cc. of a molar solution of bromine in glacial acetic acid to a solution of 22.5 g. (0.10 mole) in 800 cc. of glacial acetic acid at room temperature. After standing several hours, the solution was diluted largely with water. The filtered product was extracted by boiling with 800 cc. of alcohol, then filtered hot. The insoluble residue, 7.1 g., melted at 225-232°; recrystallization from glacial acetic acid yielded 5.0 g., 16.4%, of 2-acetamino-3-bromodibenzofuran melting at 240-241° (2). In removing the acetyl group the writer preferred alkaline hydrolysis to the alcoholic hydrochloric acid procedure of Bywater (2). Five and three-tenths grams (0.017 mole) of 2-acetamino-3-bromodibenzofuran was refluxed for two hours with a solution of 15 g. of potassium hydroxide in 130 cc. of alcohol and 20 cc. of water, then diluted with 130 cc. of hot water. On cooling, 4.3 g., a 96% yield, of crystalline 2-amino-3-bromodibenzofuran melting at 172-173° was obtained.

Diazotization of 2-amino-3-bromodibenzofuran was accomplished according to the method of Misslin (21). The well powdered amine, 4.3 g. (0.0164 mole), was added slowly with stirring to a solution of 1.19 g. of sodium nitrite in

(20) Bywater, W.G., Doctoral Dissertation, Iowa State College, 1934.

(21) Misslin, Helv. Chim. Acta, 3, 626 (1910).

100 cc. of concentrated sulfuric acid cooled to 0°. Forty grams of ice was added slowly with stirring. After allowing the reaction mixture to stand in an ice bath for three hours, it was poured over 500 g. of ice, diluted with 500 cc. of water, and allowed to stand in the ice box overnight. The diazonium sulfate solution was allowed to warm up to room temperature and filtered from a small amount of brownish insoluble material.

Conversion of the diazonium group to hydroxyl was carried out in a manner similar to that employed by Tatematsu and Kubota (3) in the preparation of 2-bromo-3-hydroxydibenzofuran. The diazonium sulfate solution was added slowly to a boiling solution of 150 g. of copper sulfate in 300 g. of water contained in a one-liter distilling flask. The distillation was continued at such a rate that the volume of liquid in the flask remained constant. 2-Hydroxy-3-bromodibenzofuran steam distilled and gathered in the condenser, from which it was removed from time to time. The crude product, 1.05 g. melting at 130-133°, was dissolved in warm 10% sodium hydroxide solution, filtered, and acidified with hydrochloric acid. The 0.85 g. of phenolic product thus obtained was recrystallized from 30 cc. of 50% alcohol to give 0.6 g., a 13% yield, of colorless needles melting at 143-144°. This bromophenol gave no color with ferric chloride in alcohol solution.

Anal. Calcd. for $C_{12}H_7O_2Br$: Br, 30.39. Found: Br, 30.66 and 30.71.

Preparation of 2-Methoxy-3-bromodibenzofuran.

Two-tenths gram of the 143-144° melting 2-hydroxy-3-bromodibenzofuran was dissolved in 30 cc. of 10% sodium hydroxide and treated with an excess of dimethyl sulfate with shaking, then allowed to stand on a water bath for one hour. The 0.1 g. of product obtained was recrystallized from alcohol to give white needles melting at 172°. This product was identical with the 172° melting bromination product of 2-methoxydibenzofuran, as a mixed melting point showed no depression.

Preparation of 2-allyloxydibenzofuran.

In accordance with Claisen's general method for preparing allyl ethers (5b), 21.7 g. (0.118 mole) of 2-hydroxydibenzofuran, 17.9 g. (0.130 mole) of anhydrous potassium carbonate, 15.7 g. (0.130 mole) of allylbromide, and 30 cc. of acetone were placed in a 300 cc. Erlenmeyer flask fitted with an efficient condenser and refluxed gently on a water bath for six hours. Water was then added to dissolve the solid residue and the solution extracted with ether. The ether layer was separated and twice extracted with 10% sodium hydroxide to remove any unchanged phenol. After drying over anhydrous potassium carbonate, the solvent was removed and the allyl ether distilled under reduced pressure. Nineteen and three-tenths grams, a 72% yield, of a heavy yellow liquid distilling at 178-180° / 4mm. was obtained. In another run the yield was 82%. No allyl ether rearrangement took place during the distillation as is sometimes the case (5b),

for the distillate was insoluble in dilute sodium hydroxide.

The constants, n_D^{25} 1.6248, and d_4^{25} 1.1553, give a found molar reactivity of 68.53 while theory requires a value of 65.09, an exaltation of 3.44 units being exhibited.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.32; H, 5.40. Found: C, 80.32; H, 5.45.

Rearrangement of 2-Allyloxydibenzofuran.

According to Claisen's general method for rearranging allyl ethers (5b), 36.8 g. (0.164 mole) of 2-allyloxydibenzofuran was placed in a 50 cc. Erlenmeyer flask equipped with a small air condenser through which a thermometer was lowered until the bulb was immersed in the liquid. The flask was placed in a metal bath in which a thermometer was suspended. The metal bath was heated with a small flame. As the temperature of the metal bath increased, the temperature of the liquid also increased but with a lag of about ten degrees. When the outer temperature reached 220°, an exothermic reaction occurred, the inner temperature rising rapidly to 230°. The outside temperature was raised to 230° and held there for fifteen minutes. On cooling, a quantitative yield of dilute alkali soluble product was obtained. Acidification of the alkaline solution with hydrochloric acid yielded a gray solid melting at about 75°. Three recrystallizations of the crude product from petroleum ether (b.p. 60-68°) gave 15.4 g., a 34% yield, of beautiful colorless needles melting at 82-83°. Further

recrystallization from petroleum ether resulted in a constant melting point of 83°. In another run, the crude product was first purified by vacuum distillation, the material distilling constantly at 173° / 5mm. Isomers were searched for but not found.

According to Claisen's rule (5d), this allyl-phenol must be either 1-allyl- or 3-allyl-2-hydroxydibenzofuran. It is shown below that the allyl group is not in the 3-position, hence it must be in the 1-position. No coloration was shown by this allyl-phenol on the addition of ferric chloride to an alcohol solution.

Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.32; H, 5.40. Found: C, 80.51; H, 5.50.

Methylation of 1-Allyl-2-hydroxydibenzofuran.

Six and seventy two-hundredths grams (0.03 mole) of 83° melting 1-allyl-2-hydroxydibenzofuran was dissolved in a solution of 4.0 g. of sodium hydroxide in 100 cc. of water, then 7.4 cc. of dimethyl sulfate was added in several portions with vigorous shaking. After allowing the reaction to stand one hour, the precipitated white solid was filtered off and washed with water. Seven and four-tenths grams, a quantitative yield, of 1-allyl-2-methoxydibenzofuran melting at 66-66.5° was obtained. Several recrystallizations from petroleum ether (b.p. 28-38°) gave large prismatic crystals melting at 67-68°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.93. Found:

C, 80.42; H, 5.62.

Allylation of 2-Methoxy-1-dibenzofurylmagnesium Bromide.

While most alkyl halides do not react with the Grignard reagent, Tiffeneau (22) found that allyl bromide and other α,β -unsaturated halides couple smoothly with it.

Accordingly, the Grignard reagent of the 117-118° melting 1-bromo-2-methoxydibenzofuran was prepared by reacting 13.8 g. (0.05 mole) of the bromo-methoxy derivative, 2.43 g. of 40-80 mesh magnesium, one-half cc. of *n*-butyl bromide, and a crystal of iodine in a solution of 75 cc. of anhydrous ether and 75 cc. of dry benzene in an atmosphere of dry nitrogen. The reaction started readily after a few minutes of heating; after spontaneous refluxing subsided, heating over a hot plate was continued for one hour. On cooling, the Grignard reagent was transferred under dry nitrogen through a plug of glass wool into a 250 cc. three-necked flask equipped with a mercury-sealed stirrer, condenser, and a dropping funnel. An excess of allyl bromide, 12.5 cc., was added dropwise with stirring. A slight warming was noticed. After refluxing for one hour, the reaction mixture was hydrolyzed by pouring on ice and hydrochloric acid; the ether layer separated and washed with water and 10% sodium hydroxide, then dried over anhydrous sodium sulfate. After removal of ether and excess allyl bromide, the product was

(22) Tiffeneau, Compt. rend., 139, 482 (1904).

distilled under reduced pressure. Eight and eight-tenths grams, a 74% yield, of oil distilling at 155-161°/ 4-5mm. was obtained. This oil soon turned to a solid melting at 60-65°. Two recrystallizations of this solid from petroleum ether (b.p. 28-38°) yielded colorless massive prisms melting at 67-68°. This compound was found to be identical by the method of mixed melting point with the 67-68° melting allyl-2-methoxydibenzofuran obtained by the Claisen allyl ether rearrangement of 2-allyloxydibenzofuran and subsequent methylation.

According to Claisen's rule (5d), rearrangement of 2-allyloxydibenzofuran can yield only 1- ^{OR} and 3-allyl-2-hydroxydibenzofuran. But this allyl-methoxy derivative came not from the authentic 172° melting 2-methoxy-3-bromodibenzofuran, but from its 117-118° melting isomer. It is clear by the method of exclusion that only the 1-position can be involved, and the structure of the above compound, therefore, is 1-allyl-2-methoxydibenzofuran.

Preparation of 1-Propenyl-2-hydroxydibenzofuran.

In accordance with the directions given by Claisen (5c) for the allylic rearrangement of *o*-allylphenol to *o*-propenylphenol, 2.0 g. (0.009 mole) of 1-allyl-2-hydroxydibenzofuran was dissolved in 6 cc. of a saturated methyl alcoholic solution of potassium hydroxide in a 25 cc. Erlenmeyer flask. About one-half of the methyl alcohol was removed by distillation, then the flask was placed in an oil bath and refluxing continued at

160-170° for two hours. The reaction mixture was dissolved in water and the solution filtered hot. On acidification with hydrochloric acid, 1.9 g. of an amorphous solid melting at 86-90° was obtained. Three recrystallizations from petroleum ether (b.p. 60-68°) followed by one from dilute methyl alcohol yielded white needles melting at 94-95°. This phenol gave no coloration with ferric chloride in alcohol solution.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 80.32; H, 5.40. Found: C, 80.27; H, 5.37.

Preparation of 2-Methoxy-3-allyldibenzofuran.

The Grignard reagent of the 172° melting 2-methoxy-3-bromodibenzofuran was made in the customary manner by reacting 13.8 g. (0.05 mole) of the halide, 2.4 g. of magnesium turnings in a mixture of 75 cc. of anhydrous ether and 75 cc. of dry benzene. In order to start the reaction, it was necessary to add a little *n*-butylmagnesium bromide. After refluxing for one hour, the solution was filtered from the magnesium into another flask, and an excess of allyl bromide (0.07 mole) was added slowly, then refluxing was continued another hour. The reaction mixture was hydrolyzed by pouring into ice and dilute sulfuric acid. The ether-benzene layer was washed with water, then dried over anhydrous sodium sulfate. After removal of the solvent, the product was distilled under reduced pressure. Seven and nine-tenths grams, a 60% yield, of a heavy yellow oil distilling at 155-159°/ 4mm. was obtained. This oil did

not solidify on standing. In order to make sure that no volatile impurity as 2-methoxydibenzofuran was present to impede solidification, the oil was subjected to steam distillation, and a small amount of volatile impurity went over. When the steam distillate was clear, the residual oil was taken up in ether, dried over anhydrous sodium sulfate, and redistilled. This time the product distilled more constantly at 158-159°/ 4mm. However, no solidification of this oil took place, even after long standing in the ice box.

Theory requires a molar refractivity of 69.51, while the determined constants, n_D^{25} , 1.6261 and d_4^{25} , 1.1488, give a found molar refractivity of 73.38, an exaltation of 3.87 units. This exaltation is in the same order of magnitude as that of 2-allyoxydibenzofuran which was found to be 3.44 units.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 80.64; H, 5.93. Found: C, 80.03 and 79.90; H, 5.79 and 5.75.

Preparation of 1-Hydroxy-2-methoxydibenzofuran.

Ivanoff (23) showed that the presence of alkylmagnesium halides catalyzed the oxidation of arylmagnesium halides, resulting in an improved yield of the phenol.

Accordingly, the Grignard reagents of 1-bromo-2-methoxydibenzofuran and n-butyl bromide were prepared simultaneously by reacting in the customary manner 42.4 g. (0.15 mole) of the

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

former halide dissolved in 75 cc. of dry benzene, one equivalent, 20.6 g. of the latter dissolved in 100 cc. of dry ether, and 10 g., of magnesium turnings. After the final refluxing to complete the formation of the Grignard reagents, the solution was cooled to 0° in an ice-salt bath. Dry oxygen was passed over the surface of the solution at 1-2 bubbles per second with stirring until a negative color test was obtained. The reaction mixture was hydrolyzed by filtering through glass wool into ice and hydrochloric acid. The ether-benzene layer was extracted with two 100 cc. portions of 10% sodium hydroxide, and the alkaline solution washed with ether. The alkaline solution was warmed to expel the dissolved ether and filtered hot. Acidification with hydrochloric acid yielded 22.9 g. of crude 1-hydroxy-2-methoxydibenzofuran as a brown amorphous solid melting at 108-110°. The yield of phenol for this type of reaction was unusually good, being 71%. Recrystallization from 30% alcohol gave a light tan crystalline solid melting at 110-111° while a further recrystallization from petroleum ether (b.p. 60-68°) resulted in colorless needles melting at 111-111.5°.

Anal. Calcd. for $C_{13}H_{10}O_2$: C, 72.87; H, 4.71. Found: C, 72.88; H, 4.61.

1-Hydroxy-2-methoxydibenzofuran in alcohol solution gives a reddish color with ferric chloride. It is also rather unstable in alkaline solution, a deep brown color being developed and a dark brown insoluble substance being deposited slowly.

Reasoning by analogy with β -methoxy- α -naphthol (23b), this instability in alkali is indicative of the ortho relationship of the two substituent groups. 1-Hydroxy-4-methoxydibenzofuran, described later, does not exhibit this instability in alkali.

An unsuccessful attempt was made to prepare 1,2-dihydroxydibenzofuran by hydriodic acid cleavage of the methoxyl group. Only an alkali insoluble purple resin was obtained.

Preparation of 1,2-Dimethoxydibenzofuran.

This compound was prepared for its possible value for reference purposes in the determination of orientation of 1-substituted derivatives. One and sixty five-hundredths grams (0.0077 mole) of 1-hydroxy-2-methoxydibenzofuran, 1.75 g. (0.0125 mole) of anhydrous potassium carbonate, 0.93 cc. of methyl iodide, and 5 cc. of acetone were placed in a 125 cc. Erlenmeyer flask equipped with an efficient condenser and refluxed on a water bath for eight hours. The product was taken up in ether, then steam distilled. One and forty seven-hundredths grams (an 83% yield) of a white crystalline substance melting at 75-79° was obtained. One recrystallization from petroleum ether (b.p. 28-38°) yielded colorless crystals melting sharply at 79°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 73.65; H, 5.30. Found: C, 73.23; H, 5.13.

(23b) Bezdzik and Friedlander, Monatsh., 30, 283 (1909).

Preparation of 1-Carboxy-2-methoxydibenzofuran.

The Grignard reagent of 36.6 g. (0.15 mole) of 1-bromo-2-methoxydibenzofuran in 300 cc. of 1:1 ether and benzene solution was made in the customary manner, the addition of one cc. of *n*-butyl bromide being required to start the reaction. Carbonation was effected by filtering the Grignard solution under dry nitrogen into an excess of solid carbon dioxide. The addition product was hydrolyzed by adding ice and hydrochloric acid. The acid, being rather insoluble in the ether-benzene solution, was filtered off directly, washed with dilute hydrochloric acid, then taken up in warm dilute sodium hydroxide solution. The filtered solution was acidified with hydrochloric acid. In this manner, 17.2 g. of acid melting at 152-157° was obtained. Alkali extraction of the ether-benzene layer yielded an additional 7.8 g. The total crude yield was 25 g. or 70%. Several recrystallizations from benzene yielded white needles melting at 156-157°.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.40; H, 4.16. Found: C, 69.37; H, 4.05.

R. L. Bebb, in this laboratory, found this acid to be identical with one of the two acids which he obtained by *n*-butyl-lithium metalation of 2-methoxydibenzofuran and subsequent carbonation. The methyl ester was prepared by him and found to melt at 99.5-100°.

Preparation of 2-Methoxy-3-carboxydibenzofuran.

The Grignard reagent of 20 g. (0.072 mole) of 2-methoxy-5-bromodibenzofuran in 150 cc. of a 1:1 mixture of anhydrous ether and dry benzene was made in the customary manner, a little *n*-butylmagnesium bromide being added to start the reaction. After carbonation with dry ice and hydrolysis with dilute hydrochloric acid, the solid acid was found insoluble in the ether-benzene solution, so it was filtered off directly. Ten and one-half grams, a 60% yield, of white solid melting at 204-207° was obtained. Recrystallization from 500 cc. of alcohol gave 8.8 g. of needles melting at 206-207°. An additional recrystallization from 700 cc. of toluene did not raise the melting point.

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 69.40; H, 4.16. Found: C, 69.22; H, 4.05.

This acid was found by R. L. Bebb, in this laboratory, to be identical with a second acid obtained by *n*-butyl-lithium metalation of 2-methoxydibenzofuran and subsequent carbonation. The methyl ester, prepared by him, melted at 122.5°.

Preparation of 2-Methoxy-8-bromodibenzofuran.

This compound was prepared by the diphenyl ether ring closure method employed by McCombie and co-workers (4) in the synthesis of 2-chloro-, 2- and 3-bromo-, 2,8-dichloro-, 2,8-dibromo-, 2,7-dibromo-, and 2-chloro-7-nitrodibenzofurans.

The monomethyl ether of hydroquinone was prepared according to the directions of Tieman and Miller (24). The potassium (24) Tieman and Miller, Ber., 14, 1989 (1881).

salt was made by adding a calculated quantity of potassium hydroxide to a methyl alcohol solution of the *p*-methoxyphenol and throwing out the salt by diluting with ether.

2-Nitro-4-bromo-4'-methoxydiphenyl ether was prepared by heating directly in a 250 cc. Erlenmeyer flask immersed in an oil bath 8.8 g. (0.054 mole) of potassium *p*-methoxyphenoxide and 15.26 g. (0.054 mole) of nitro-*p*-dibromobenzene at 170° for two hours. On cooling, the crude product was extracted with ether and unreacted nitro-*p*-dibromobenzene (2.2 g.) removed by steam distillation. The residual oily substance was taken up again in ether, dried over sodium sulfate, and the ether removed by distillation. An oily residue of 12.9 g. (0.04 mole) was obtained.

Reduction of the crude 2-nitro-4-bromo-4'-methoxydiphenyl ether was accomplished by dissolving the crude ether and 29.6 g. of stannous chloride in 300 cc. of ether, cooling in an ice bath, and introducing a stream of dry hydrogen chloride just under the surface of the ether solution for three hours with stirring. The ether solution was transferred to a one-liter Erlenmeyer flask, cooled in an ice-salt bath, and detinned by cautious addition, with shaking, of ice-cold 30% sodium hydroxide solution. When both layers were clear, the ether solution was washed with water and the amine extracted with several 100 cc. portions of 10% hydrochloric acid.

The hydrochloric acid solution of the amine hydrochloride was cooled to 0° and diazotized by adding 10% sodium nitrite

solution until a positive starch-potassium iodide test was obtained.

Ring closure was effected by adding the diazonium chloride solution dropwise to 200 cc. of boiling 50% sulfuric acid solution contained in a 500 cc. distilling flask. A white solid began immediately to collect in the condenser. Water was added from time to time to keep the volume of liquid constant. Distillation was continued until no more solid came over. The white solid (1.2 g.) melting at 70-80° was treated with hot dilute sodium hydroxide to remove any phenolic products that might have been formed. The product was then recrystallized from dilute alcohol, and a colorless crystalline substance melting sharply at 92.5° was obtained. The purified yield was 0.94 g. or 8%, based on the crude nitrodiphenyl ether derivative.

To demonstrate that a dibenzofuran compound had been formed, the ring closure product was dehalogenated catalytically (24a). One-tenth gram of the ring closure product was dissolved in 25 cc. of 10% methyl alcoholic potassium hydroxide, and 0.5 g. of palladium-calcium carbonate catalyst added. The suspension was shaken for two hours in an Adams hydrogenation apparatus under a pressure of 34 pounds of hydrogen. After filtering, the alcoholic solution was steam distilled. An oil came over, which on standing in the ice box, deposited crystals melting at 44-45°. This solid was found identical,

(24a) Borsche and Stowe, Ber., 49, 1063 (1916).

by mixed melting point, with the 46-47° melting 2-methoxydibenzofuran. This fact and consideration of the mode of synthesis lead to the conclusion that the ring closure product can be only 2-methoxy-8-bromodibenzofuran (25).

Anal. Calcd. for $C_{12}H_8BrOCH_3$: Br, 28.85; OCH_3 , 11.19.
Found: Br, 29.21 and 29.25; OCH_3 , 11.10 and 10.90.

Bromination of 4-Hydroxydibenzofuran.

4-Hydroxydibenzofuran has been prepared in 35% crude yield by the oxidation of 4-dibenzofurylsodium (26). The writer obtained a crude yield of 20-25% by the oxidation of 4-dibenzofuryl-lithium. However, applying the modification of Ivanoff (23), it was found that the addition of one equivalent of *n*-butylmagnesium bromide prior to oxidation increased the yield of crude phenol to 35%.

In the bromination, 5.52 g. (0.03 mole) of 101-102° melting 4-hydroxydibenzofuran was dissolved in 60 cc. of glacial acetic acid. To this solution at room temperature was added 30 cc. of a molar solution of bromine in glacial acetic acid. The bromine was taken up readily. After allowing to stand one hour, the solution was diluted with 160 cc. of water, and the solid that separated was filtered off. Six and eight-tenths grams, an 83% yield, of crude tan colored product melting at

(25) The writer is indebted to W.M. Hoehn for the micro-Zeisel analysis of this compound.

(26) Gilman and Young, J. Am. Chem. Soc., 57, 1121 (1935).

137-146° was obtained. Decolorization with norite and recrystallization from dilute alcohol gave 5.5 g. of white needles melting at 145-147°. Two recrystallizations from benzene yielded 3.8 g., a 35% yield, of long colorless needles melting at 151.5-152°. This compound in alcohol gave no color test with ferric chloride. This monobromo derivative is very probably 1-bromo-4-hydroxydibenzofuran.

Anal. Calcd. for $C_{13}H_7O_2Br$: Br, 30.39. Found: Br, 30.71 and 30.80.

Methylation of 1-Bromo-4-hydroxydibenzofuran.

1-Bromo-4-hydroxydibenzofuran, 1.15 g., (0.0043 mole), was dissolved in 30 cc. of methyl alcohol and 100 cc. of 5% sodium hydroxide solution added. An excess of dimethyl sulfate was added with shaking and the solution allowed to stand on a water bath one hour. Ninety eight-hundredths gram (an 81% yield) of 1-bromo-4-methoxydibenzofuran melting at 96-97° was obtained. Two recrystallizations from alcohol gave colorless needles melting at 97-97.5°.

Anal. Calcd. for $C_{13}H_9O_2Br$: Br, 28.85. Found: Br, 29.10 and 29.15.

Preparation of 1-Bromo-4-methoxydibenzofuran.

Bromination of 4-methoxydibenzofuran was found by P.T. Parker, in this laboratory, to go smoothly giving an excellent yield of bromo-4-methoxydibenzofuran identical with that prepared by methylation of 1-bromo-4-hydroxydibenzofuran.

Twenty-seven and five-tenths grams (0.139 mole) of 4-methoxydibenzofuran (26) was dissolved in 200 cc. of glacial acetic acid, and brominated by adding 139 cc. of a molar solution of bromine in glacial acetic acid. After allowing the solution to stand for one hour, it was diluted with water and the precipitate was filtered off. The crude material was dissolved in 300 cc. of hot alcohol; on cooling, 33 g., an 86% yield, of colorless needles melting at 97-98° was obtained. The high yield and ease of purification of this compound indicate that there is very little if any isomer formation in the bromination of 4-methoxydibenzofuran.

Preparation of 1-Hydroxy-4-methoxydibenzofuran.

The Grignard reagent of 27.7 g. (0.10 mole) of 1-bromo-4-methoxydibenzofuran was prepared by refluxing 2.7 g. of magnesium turnings in 200 cc. of a 1:1 mixture of anhydrous ether and dry benzene. The addition of one cc. of *n*-butyl bromide was necessary to start the reaction. One equivalent of *n*-butylmagnesium bromide was then added, the reaction mixture cooled to 0°, and oxidation effected by passing in dry oxygen gas at the rate of about two bubbles per second. At the appearance of a negative color test, the addition product was hydrolyzed by filtering the solution through a plug of glass wool into a mixture of ice and hydrochloric acid. After washing with water, the ether-benzene layer was extracted twice with 10% sodium hydroxide solution. Acidification of the alkaline solution with hydrochloric

acid yielded 8.5 g., a 39% yield, of brown solid melting at 145-150°. The crude product was decolorized with norite in alcohol solution, and recrystallized twice from 10% alcohol to give colorless needles melting sharply at 155°. An alcohol solution of this compound gave a green coloration with ferric chloride. It is also much more stable in alkaline solution than the corresponding 1-hydroxy-2-methoxydibenzofuran.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.87; H, 4.71. Found: C, 72.75; H, 4.73.

Preparation of 1,4-Dihydroxydibenzofuran.

Two-tenths of a gram of 1-hydroxy-4-methoxydibenzofuran was cleaved by refluxing two hours with 5 cc. of constant boiling hydriodic acid in the presence of a small amount of red phosphorus. On dilution with water a brownish solid separated out. This solid was taken up with dilute sodium hydroxide, filtered, and reprecipitated with hydrochloric acid. The crude brown solid melting at 200-210° was recrystallized twice from water to give a small amount of light tan crystalline solid melting at 217-218° with decomposition. A deep yellow coloration was produced by adding ferric chloride to an alcohol solution.

Anal. Calcd. for $C_{12}H_8O_3$: C, 71.96; H, 4.03. Found: C, 72.20; H, 4.18.

Preparation of 1,4-Dimethoxydibenzofuran.

Five grams (0.0233 mole) of 1-hydroxy-4-methoxydibenzofuran was dissolved in dilute sodium hydroxide solution (1.4 g. (0.035

mole) of sodium hydroxide in 150 cc. of water) and 2.8 cc. (0.03 mole) of dimethyl sulfate was added with shaking. The product that separated was steam distilled with superheated steam. The 2.9 g., a 54% yield, of solid obtained from the distillate melted at 77-77.5°. Recrystallization from petroleum ether (b.p. 60-68°) gave 2.1 g. of colorless prisms melting sharply at 78.5°.

Anal. Calcd. for $C_{11}H_{11}O_2$: C, 73.65; H, 5.30. Found: C, 73.96; H, 5.24.

Preparation of 4-Aminodibenzofuran.

4-Aminodibenzofuran has been made by W.G. Bywater (20, 27) by amination of 4-hydroxydibenzofuran with zinc chloride and ammonium chloride, and by the Hofmann degradation of 4-dibenzofurancarboxylic acid amide, the yield in the former case being 16%, and in the latter 30-50%, based on the amide actually used up.

L.C. Cheney, in this laboratory, has developed a method for preparing the 4-amine by amination of 4-bromodibenzofuran with ammonium hydroxide and cuprous chloride in a steel bomb at 190-200°. His yield of pure amine was 50-60%.

The writer has employed a modified Hofmann reaction adapted from Jeffreys' procedure (28) for preparing *p*-nitroaniline from *p*-nitrobenzamide. The reaction is carried out in methyl

(27) Kirkpatrick and Parker, J. Am. Chem. Soc., 57, 1126 (1935).
(28) Jeffreys, Am. Chem. J., 22, 14 (1899).

alcohol solution, the methyl urethane being formed. The urethane is converted to the amine by heating with four times its weight of slaked lime.



Ten and six-tenths grams (0.05 mole) of 4-dibenzofuran-carboxylic acid amide prepared according to directions of W.G. Bywater (20) was suspended in 100 cc. of methyl alcohol. To this was added the sodium methoxide solution prepared by dissolving 2.3 g. (0.1 g. atom) of sodium in 60 cc. of methyl alcohol. Bromine, 8.0 g. (0.05 mole), was then added slowly with shaking, whereupon practically all the solid went rapidly into solution. To complete the reaction, the solution was refluxed for one-half hour. During the refluxing, a precipitate of the urea appeared which caused vigorous bumping. This was filtered off and refluxing continued. The solution containing the methyl urethane was poured over 38 g. of calcium hydroxide in a large evaporating dish, and allowed to stand on the steam plate until dry. To the dry lime mixture was added the 2.1 g. of the urea previously obtained, and the whole mixture thoroughly pulverized. The dry powdered solid was placed in a 125 cc. Erlenmeyer flask and heated in an oil bath for one and one-half hours at 200-210°. The light brown colored contents were then

extracted with ether and the amine hydrochloride precipitated with dry hydrogen chloride. The amine hydrochloride (6.5 g.) was dissolved in hot water, filtered, and on cooling to 60°, the amine was thrown out by the addition of an excess of ammonium hydroxide. The yield of partially pure amine melting at 80-81° was 5.0 g. or 54.4%. In several one-tenth mole runs, worked up together, the yield of amine was 56.7%.

Bromination of 4-Acetaminodibenzofuran.

Twenty-two and five-tenths grams (0.1 mole) of 4-acetaminodibenzofuran (27), prepared by acetylating the amine in benzene solution with acetic anhydride, was dissolved in 300 cc. of glacial acetic acid, and 100 cc. of a molar solution of bromine in glacial acetic acid added slowly with stirring. The bromine was taken up readily and a yellow precipitate appeared. After allowing to stand for one hour, the reaction mixture was diluted with water to one liter and the product filtered off. A quantitative yield, 31.1 g., of monobrominated derivative melting at 222-224° was obtained. Several recrystallizations from toluene yielded a crystalline solid of pearly luster melting at 228°. This compound is very probably 1-bromo-4-acetaminodibenzofuran.

Anal. Calcd. for $C_{14}H_{10}O_2NBr$: Br, 26.26. Found: Br, 26.23 and 26.41.

Hydrolysis of 1-Bromo-4-acetaminodibenzofuran.

Twenty one and four-tenths grams (0.07 mole) of

1-bromo-4-acetaminodibenzofuran was refluxed two hours in a solution of 40 g. of potassium hydroxide in 400 cc. of alcohol. The solution was then diluted with 400 cc. of hot water. On cooling in the ice box, 16.2 g., an 89% yield, of 1-bromo-4-aminodibenzofuran melting at 118-118.5° was obtained. A further recrystallization from dilute alcohol followed by one from a mixture of benzene and petroleum ether (b.p. 60-68°) gave fine colorless needles melting at 119-120°. The high yield of relatively pure crude product is indicative of the smoothness of bromination and absence of isomer formation.

Anal. Calcd. for $C_{12}H_{11}ONBr$: Br, 30.51. Found: Br, 30.82.

Conversion of 1-Bromo-4-aminodibenzofuran to 1-Bromo-4-hydroxy-dibenzofuran.

Six-tenths of a gram (0.0025 mole) of 1-bromo-4-aminodibenzofuran was diazotized by adding the well powdered amine to a solution of 0.17 g. of sodium nitrite in 75 cc. of concentrated sulfuric acid cooled to 0°. The solution was diluted by the addition of 40 g. of ice, allowed to stand one hour, then poured over 450 g. of ice. The solution was filtered away from a small amount of insoluble residue and added dropwise to a boiling solution of 75 g. of copper sulfate in 300 cc. of water contained in a 500 cc. distilling flask. The distillation was continued, the volume being held constant, until no more solid came over. Of the crude bromo-phenol, 0.15 g., a 25% yield, melting at 147-150° was obtained. Recrystallization from

benzene and petroleum ether (b.p. 60-68°) gave a melting point of 152°. This compound was found by mixed melting point to be identical with the 151.5-152° melting bromination product of 4-hydroxydibenzofuran.

Preparation of 1-Bromodibenzofuran.

Thirteen and one-tenth grams (0.05 mole) of 1-bromo-4-aminodibenzofuran (m.p. 118-119°) was boiled with 600 cc. of 10% hydrochloric acid to form the hydrochloride. The suspension of the hydrochloride was cooled to 0°, and diazotized by the addition of 3.83 g. of sodium nitrite dissolved in 50 cc. of water. The solution was allowed to stand one hour in an ice bath.

Removal of the diazonium chloride group was accomplished by the method of Mai (29). To the ice-cold suspension of the yellow crystalline diazonium chloride was added 80 cc. of 50% hypophosphorous acid, whereupon nitrogen began slowly to be evolved. The reaction was completed by allowing to stand three days in the ice box with occasional shaking. The grayish yellow solid was filtered off and steam distilled. Nine and sixty six-hundredths grams, a 78% yield, of colorless 1-bromodibenzofuran melting at 65-67° was obtained. Several recrystallizations from petroleum ether (b.p. 28-38°) gave large prisms melting constantly at 67°. By the method of exclusion, this compound

(29) Mai, Ber., 35, 162 (1902).

was proven to be 1-bromodibenzofuran. In a mixed melting point with the 72° melting 4-bromodibenzofuran, a depression was noted.

Anal. Calcd. for $C_{12}H_9OBr$: Br, 32.35. Found: Br, 32.30 and 32.11.

Preparation of 1-Aminodibenzofuran.

Two grams (0.008 mole) of 1-bromodibenzofuran was aminated by heating in a sealed tube with 2 g. of cuprous bromide and 10 cc. of concentrated ammonium hydroxide at 230-240° for ten hours. On cooling, the contents of the tube were extracted with ether, the ether solution washed with water and dried over anhydrous sodium sulfate. Of the amine hydrochloride, precipitated with dry hydrogen chloride, 0.43 g. was obtained. This was dissolved in 30 cc. of hot 2% hydrochloric acid; the solution was decolorized with norite, and filtered hot. The free amine was precipitated in grayish white needles by addition of ammonium hydroxide. The yield of crude amine melting at 72-73° was 0.3 g. or 24%. One recrystallization from dilute methanol furnished white needles melting at 74°.

Anal. Calcd. for $C_{12}H_9ON$: N, 7.65. Found: N, 7.84 and 7.86.

While the 2-, 3-, and 4-aminodibenzofurans are without odor, it is interesting to note that the 1-amine does possess a slight odor similar to that of α -naphthylamine. Pharmacological tests carried out in the laboratory of Parke-Davis Co.

reveal that 1-aminodibenzofuran hydrochloride has an analgesic action similar in degree to that of acetylsalicylic acid.

Preparation of 1-Acetaminodibenzofuran.

One-tenth of a gram of 1-aminodibenzofuran was dissolved in a small amount of warm petroleum ether (b.p. 60-68°) and a slight excess of acetic anhydride added. In a short time, 1-acetaminodibenzofuran was precipitated as a white amorphous solid melting at 205°. Recrystallization from 70% alcohol yielded fine white needles melting sharply at 205°.

Anal. Calcd. for $C_{14}H_{11}O_2N$: N, 6.22. Found: N, 6.38 and 6.40.

Preparation of 1-Hydroxydibenzofuran.

1-Dibenzofurylmagnesium bromide was prepared in the presence of one equivalent of *n*-butylmagnesium bromide by reacting in the customary manner 9.56 g. (0.039 mole) of 1-bromodibenzofuran, 4.3 cc. of *n*-butyl bromide, and 5 g. of magnesium turnings in a mixture of 70 cc. of anhydrous ether and 70 cc. of dry benzene. In order to ascertain the formation of the aryl Grignard reagent, 1 cc. of the solution was hydrolyzed and steam distilled to yield a small amount of dibenzofuran. Oxidation was effected by passing dry oxygen into the well stirred, ice-salt cooled reaction mixture until a negative color test was obtained. The reaction mixture was filtered through a plug of glass wool into dilute hydrochloric acid, and the ether-benzene layer washed

with water. The phenol was taken up in dilute sodium hydroxide and precipitated by the addition of hydrochloric acid. The yield of light tan colored 1-hydroxydibenzofuran melting at 138.5-140° was 2.42 g. or 31%. Recrystallization from about a liter of water furnished a gray crystalline solid melting at 140-140.5°. Of the 2-, 3-, and 4-hydroxydibenzofurans, the one melting closest to 1-hydroxydibenzofuran is 3-hydroxydibenzofuran (m.p. 137-138°). On taking a mixed melting point of the latter material with 1-hydroxydibenzofuran, a depression of ten degrees was noted. In alcohol solution, 1-hydroxydibenzofuran gave a purple color on addition of ferric chloride.

Anal. Calcd. for $C_{12}H_8O_2$: C, 78.24; H, 4.38. Found: C, 78.54; H, 4.53.

Bromination of 1-Hydroxydibenzofuran.

Two and four-tenths grams (0.013 mole) of 1-hydroxydibenzofuran was dissolved in 50 cc. of glacial acetic acid and 13 cc. of a molar solution of bromine in glacial acetic acid was added at room temperature. The bromine was taken up immediately. The solid product, 3.42 g., which came down on dilution with water represented a quantitative yield of crude bromo-1-hydroxydibenzofuran melting at 94-145°. This was refluxed with 150 cc. of 50% alcohol and all went into solution except a small amount of grayish residue. On cooling, 2.2 g. of a white crystalline substance melting at 103-115° was obtained. Alternate recrystallizations from 1:1 benzene-petroleum ether

(b.p. 60-68°) and 50% alcohol raised the melting point to 111-118°. Further efforts to obtain from this fraction a definite compound were without avail.

On dilution of the mother liquor from the dilute alcohol recrystallization of the crude material, 1.0 g. of solid melting at 150-165° was obtained. Repeated recrystallization from benzene, with great loss involved, gave definite fine white needles melting sharply at 178°. This monobromination product is probably 1-hydroxy-2-bromo- or 1-hydroxy-4-bromodibenzofuran. The small amount available made it impracticable to attempt proof of structure by its conversion to a dimethoxy derivative for comparison with the 1,3- and 1,4-dimethoxydibenzofurans already prepared. No color was developed on treating an alcohol solution of the 178° bromination product with ferric chloride.

Anal. Calcd. for $C_{12}H_7O_2Br$: Br, 30.39. Found: Br, 30.24.

Preparation of 1-Carboxydibenzofuran.

1-Dibenzofurylmagnesium bromide was made in the customary manner from 9.88 g. (0.04 mole) of 1-bromodibenzofuran, 2 g. of magnesium turnings, and 1 cc. of n-butyl bromide in a mixture of 75 cc. of anhydrous ether and 75 cc. of dry benzene. After the final refluxing, the Grignard solution was filtered under dry nitrogen into an excess of solid carbon dioxide. The addition product was hydrolyzed by addition of ice and hydrochloric acid. The ether-benzene layer was washed with water, then extracted twice with 10% sodium hydroxide solution. Precipitation with

acid gave 7.65 g., a 90% yield, of 1-carboxydibenzofuran melting at 230-232°. After recrystallization from 50% alcohol, the acid, obtained as a white crystalline substance, melted at 232-233°. Theory requires a neutralization equivalent of 212; the found value was 207.

Anal. Calcd. for $C_{12}H_8O_3$: C, 73.58; H, 3.82. Found: C, 73.76; H, 4.07.

Preparation of 1-Carbomethoxydibenzofuran.

Esterification of 1-carboxydibenzofuran was accomplished by refluxing 7.6 g. (0.036 mole) of the acid with 100 cc. of methanol, cooling, and saturating with dry hydrogen chloride at room temperature. The solution was allowed to stand twelve hours, then was refluxed for two hours. On cooling, 5.2 g. of methyl ester melting at 62.5-63° was obtained; dilution of the mother liquor yielded an additional 2 grams. The total yield was 7.2 g. or 88%. Recrystallization from methanol furnished lustrous plates melting at 63°.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.31; H, 4.46. Found: C, 74.31; H, 4.48.

Nitration of 1-Carbomethoxydibenzofuran.

Two and one-half grams (0.011 mole) of 1-carbomethoxydibenzofuran was placed in a 50 cc. Erlenmeyer flask and 10 cc. of concentrated nitric acid (d. 1.42) added, and the reaction mixture shaken from time to time. At first an oil came down; this turned solid after about an hour. The solid was broken

up with a glass rod and the reaction allowed to stand overnight. The reaction mixture was diluted, the solid filtered and washed thoroughly with water. The crude yield of yellow solid melting at 140-181° was 2.83 grams. Four recrystallizations from glacial acetic acid were required to obtain a definite compound. The purified yield of colorless needles melting at 216° was 1.0 g. or 33%. Analysis revealed this compound to be a mono-nitro derivative.

Anal. Calcd. for $C_{14}H_9O_5N$: N, 5.17. Found: N, 5.34 and 5.43.

Hydrolysis of Nitro-1-carbomethoxydibenzofuran.

One gram (0.0037 mole) of the 216° melting nitro-1-carbomethoxydibenzofuran was refluxed three hours with 75 cc. of a 1:1 mixture of glacial acetic acid and concentrated hydrochloric acid. The reaction mixture was diluted with water and the solid filtered off. The crude acid was dissolved in warm dilute alkali, filtered hot, and reprecipitated with hydrochloric acid. The nitro-carboxylic acid thus obtained melted at 295-297°. Recrystallization from glacial acetic acid yielded fine light yellow needles melting at 297-298°.

One-tenth gram of the nitro-acid was decarboxylated by heating at 230° for twenty minutes with 2 cc. of quinoline and a trace of copper bronze. The quinoline was neutralized with dilute sulfuric acid, then the residue was steam distilled. The solid that came over melted at 178-179° and was identified

by mixed melting point as 3-nitrodibenzofuran. Hence, the nitro-acid is 3- or 7-nitro-1-carboxydibenzofuran.

Anal. Calcd. for $C_{12}H_7O_2N$: N, 5.45. Found: N, 5.45 and 5.36.

Preparation of Monobromohydroquinone.

The synthesis of 2,5-dimethoxy-2'aminodiphenyl ether for an attempted ring closure required the preparation of a number of intermediates.

Hydroquinone was brominated in accordance with the directions of Sarauw (30). One hundred ten grams (1 mole) of hydroquinone was dissolved in 900 cc. of ether, then 300 cc. of chloroform was added. One mole of bromine dissolved in 150 cc. of chloroform was added dropwise with stirring over a period of three to four hours. The solution was then evaporated in a large dish at room temperature. The crude material was ground to a powder and the monobromohydroquinone taken up by extracting six times with one-liter portions of hot petroleum ether (b.p. 77-115°). On cooling, partially pure monobromohydroquinone separated out. The yield of material melting at 105-111° was 104 g. or 55%.

Preparation of Bromo-p-dimethoxybenzene.

In accordance with the procedure of Votocek and Koehler (31), 94.5 g. (0.5 mole) of monobromohydroquinone (m.p. 105-111°)

(30) Sarauw, Ann., 209, 105 (1901).

(31) Votocek and Koehler, Ber., 46, 1767 (1913).

was dissolved in dilute alkali (48 g. of sodium hydroxide in 500 cc. of water). To this solution was added with stirring 121 cc. (1.3 mole) of dimethyl sulfate. An additional 10 g. of sodium hydroxide was added, then the reaction allowed to continue on the water bath for one hour with stirring. The crude methylation product was steam distilled. There came over first a little dimethyl ether of hydroquinone, then the desired product, and finally a small amount of the 143° melting dibromo-p-dimethoxybenzene. The middle fraction was taken up in ether, dried over anhydrous sodium sulfate, and distilled twice under reduced pressure. In this manner 57 g., a 52% yield, of a heavy yellow oil distilling at 139-142°/ 14-15mm. was obtained. The material was entirely soluble in 80% acetic acid, which differentiates it from the dibromodimethyl-ether.

Preparation of 2, 5-Dimethoxyphenol.

The Grignard reagent of bromo-p-dimethoxybenzene was made in the presence of n-butylmagnesium bromide. One hundred eight and five-tenths grams (0.5 mole) of the aryl bromide, an equivalent quantity of n-butyl bromide, and 25 g. of magnesium turnings in a mixture of 400 cc. of dry benzene and 500 cc. of anhydrous ether were reacted in the customary manner. After the final refluxing, the reaction mixture was cooled to 0° and dry oxygen was introduced at the rate of about 1-2 bubbles per second with stirring until a negative color test was obtained. The solution was filtered through glass wool into a mixture of ice

and hydrochloric acid. The benzene-ether layer was washed with water and extracted with two 100 cc. portions of 10% sodium hydroxide. The phenol was precipitated with hydrochloric acid, again taken up in ether, dried over anhydrous sodium sulfate, and distilled under reduced pressure. Thirty three grams, a 43% yield, of a light yellow oil distilling at 134-135°/ 15 mm. was obtained. It is soluble in the usual organic solvents, but insoluble in water. In 50% alcohol solution, this phenol developed a reddish brown color on the addition of ferric chloride.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.31; H, 6.54. Found: C, 62.41; H, 6.37.

The benzoate of 2,5-dimethoxyphenol, prepared by a Schotten-Baumann reaction with benzoyl chloride and recrystallized from alcohol, melted at 73.5°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 69.73; H, 5.48. Found: C, 69.33; H, 5.39.

Preparation of 2,5-Dimethoxy-2'-aminodiphenyl Ether.

Thirty-three grams (0.17 mole) of the potassium salt of 2,5-dimethoxyphenol (made in quantitative yield by reacting the phenol with potassium hydroxide in methanol solution and throwing out with ether) was mixed intimately with 41.2 g. (0.204 mole) of *o*-bromonitrobenzene in a 500 cc. Erlenmeyer flask. Coupling was effected by heating in an oil bath at 170° for two hours. The reaction mixture was extracted with

ether, the ether removed by distillation, and the residue steam distilled to remove excess *o*-bromonitrobenzene. The steam distillation residue was again taken up in ether, dried over sodium sulfate, and distilled under reduced pressure. Eighteen grams, a 38% yield, of 2,5-dimethoxy-2'-nitrodiphenyl ether distilling at 190-193°/ 3 mm. was obtained. This compound was not analyzed.

The nitro-diphenyl ether was reduced with stannous chloride. Eighteen grams (0.065 mole) of 2,5-dimethoxy-2'-nitrodiphenyl ether was dissolved in 500 cc. of ether and 53 g. (0.234 mole) of stannous chloride dihydrate added. The ether solution was cooled in an ice bath and dry hydrogen chloride passed in for two hours with stirring. The tin complex was broken up by adding slowly ice-cold 30% sodium hydroxide to the ether solution cooled in an ice-salt bath. When all the white solid at the ether-water interface had been dissolved, the ether layer was separated, washed with water, and dried over anhydrous sodium sulfate. The ether was removed and the residue distilled under reduced pressure. Seven grams, a 45% yield, of a heavy oil distilling at 183-185°/ 4 mm. was obtained. This oil on standing a short time turned to a yellow solid melting at 67-70.5°. Two recrystallizations from petroleum ether (b.p. 60-68°) yielded crystalline 2,5-dimethoxy-2'-aminodiphenyl ether melting at 72°.

Anal. Calcd. for $C_{14}H_{14}O_2N$: N, 5.74. Found: N, 5.73 and 5.99.

Attempted Ring Closure of 2,5-Dimethoxy-2'-aminodiphenyl Ether.

Three and four-tenths grams of 2,5-dimethoxy-2'-aminodiphenyl ether was dissolved in 100 cc. of 10% hydrochloric acid. The solution was cooled to 0° and diazotized with sodium nitrite solution (starch-iodide test). The diazonium chloride solution was dropped slowly into a boiling solution of 50% sulfuric acid (100 cc.) contained in a 250 cc. distilling flask, and the distillation continued. The only material that came over was an alkali soluble phenolic product. Apparently, instead of the expected coupling to give 1,4-dimethoxydibenzofuran, replacement of the diazonium group by hydroxyl occurred.

Tabulated Results of Ferric Chloride Tests

Phenol	Color
1-Hydroxydibenzofuran	Light purple
2-Hydroxydibenzofuran	Green
3-Hydroxydibenzofuran	Green
4-Hydroxydibenzofuran	Green
1-Bromo-2-hydroxydibenzofuran	None
1-Allyl-2-hydroxydibenzofuran	None
1-Propenyl-2-hydroxydibenzofuran	None
1-Hydroxy-2-methoxydibenzofuran	Red
1-Bromo-4-hydroxydibenzofuran	None
1-Hydroxy-4-methoxydibenzofuran	Green
1,4-Dihydroxydibenzofuran	Deep yellow
Bromo-1-hydroxydibenzofuran	None
2,5-Dimethoxyphenol	Reddish brown

The ferric chloride tests were carried out by dissolving the substance in a small amount of alcohol and adding a drop of ferric chloride solution. Water was then added until the solution began to be turbid.

1-Hydroxydibenzofuran gives a light purple color while the 2-, 3-, 4-hydroxydibenzofurans give a green color. This is similar to the behavior of like naphthalene derivatives, for α -naphthol gives a violet color while β -naphthol gives a green color (32).

While 1-allyl-2-naphthol and 2-allyl-1-naphthol both give a green color, 1-allyl-2-hydroxydibenzofuran gives no color. This is not surprising, as some of Claisen's allyl-phenols (5) give "weak and little characteristic colors" with ferric chloride.

(32) Meyer, Hans, "Analyse und Konstitutionsermittlung organischer Verbindungen", Julius Springer, 1931, pp. 301-302.

SUMMARY

- I. Bromination of 2- and 4-hydroxy- and 4-acetaminodibenzofurans has been investigated.
- II. Evidence is presented bearing on the structure of the brominated derivatives obtained.
- III. The preparation of a series of 1-monosubstituted dibenzofurans, the first to be reported, has been described. Substitution reactions of several of these derivatives have been accomplished.
- IV. Several ring closure syntheses of dibenzofuran derivatives have been attempted, one successfully.

INTRODUCTION

The term metalation has been proposed by Gilman and Young (1) for the reaction involving the replacement of hydrogen by a metal to give a true organometallic compound.

Much has been accomplished in this laboratory in the metalation of unsaturated heterocycles. Derivatives substituted in positions hitherto not entered by direct substitution reactions have been made available by the reaction of metalation. Thus, 4-substituted dibenzofurans have been made available by the metalation of dibenzofuran with n-butyl-lithium and mercuric acetate (1). Biologically significant 4,6-dibenzofuran derivatives have been prepared by treatment of dibenzofuran with n-butylsodium and subsequent reactions of the disodium-compound (2).

However, metalation of a given aromatic nucleus with various agents does not always involve the same position. Gilman and Kirby (3) have found that metalation of 5-ethylcarbazole with n-butyl-lithium takes place in the 4-position, while mercuration occurs in the 2-position. In addition, with a given polynuclear heterocycle, the position occupied on metalation is also dependent on the substituent groups already present. Dibenzofuran itself metalates in the 4-position, but R.L. Bebb, in unpublished work, has shown that metalation

- (1) Gilman and Young, J. Am. Chem. Soc., 56, 1415 (1934).
(2) Gilman and Kirby, J. Am. Chem. Soc., 57, 1121 (1935).
(3) Gilman and Kirby, J. Org. Chem., 1, 146, (1936).

of 2-methoxydibenzofuran involves the 1- and 3-positions.

A.L. Jacoby, in unpublished work, treated dibenzothiophene with n-butyl-lithium. Carbonation of the resulting organometallic compound gave a 55% yield of a crude monocarboxy-acid which, when purified, melted at 252-253°. The structure of this acid has not been proven; however, the possibility of 2-metalation was excluded by the preparation of authentic 2-carboxydibenzothiophene melting at 255° and which was found by the method of mixed melting points to be dissimilar from the metalation acid. Attempts to mercurate dibenzothiophene have been unsuccessful.

R.L. Bebb, in this laboratory, metalated 10-ethylphenoxazine with n-butyl-lithium. Carbonation of the organometallic compound gave a 50% yield of crude acid. Purification resulted in a monocarboxy-acid melting at 161-161.5°. There was some evidence of dimetalation, but the di-acid could not be entirely separated from the mono-acid. The structure of the monocarboxy-acid has not been proven. Attempts to mercurate 10-ethylphenoxazine were unsuccessful.

M.W. VanEss, in unpublished work, obtained a 53-61% yield of crude monocarboxy-acid by metalation of phenoxthin with n-butyl-lithium and subsequent carbonation. The structure of this metalation acid, melting at 168-169°, has not been proven; however, the possibility of 2- and 3-metalation has been excluded on the basis of the melting points of the 2- and 3-carboxyphenoxthins.

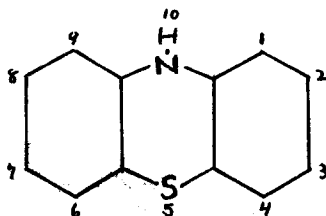
In this series of metalation studies of various polynuclear heterocycles, the writer was concerned with the nitrogen and sulfur containing heterocycle, phenothiazine. The object of this study was to determine the ease of metalation of 10-ethylphenothiazine with n-butyl-lithium and to determine, if possible, the position taken by the entering group. Furthermore, any new method of obtaining substituted phenothiazine derivatives might be useful to those interested in preparing phenothiazine derivatives for pharmacological studies.

Recently, De Eds, Thomas, Eddy, and Stockton (4) have studied the urinary antiseptic properties of phenothiazine in rabbits infected with experimental cystitis. They state, "Acute toxicity of phenothiazine is so low that fatal doses have not been determined. However, administration of very high or extratherapeutic doses produce variable degrees of fleeting anemia."

(4) De Eds, Thomas, Eddy, and Stockton, J. Pharmacol., 57, 118 (1936).

HISTORICAL

Application of the international rules for numbering ring systems (5) results in the following numbering order for phenothiazine.



A much used synonym is thiodiphenylamine, but this term is not in favor with Patterson (5). Phenothiazine is the name used by Chemical Abstracts; however, Meyer and Jacobson (6) suggest that a rational name would be dibenzoparathiazine.

An excellent review of phenothiazine and its derivatives is found in Meyer and Jacobson's "Lehrbuch" (6). The substitution reactions of phenothiazine, not particularly stressed in the Meyer and Jacobson review, will receive special attention here.

Phenothiazine was first prepared by Bernthsen (7) in the course of his proof of structure work on Lauth's violet and methylene blue. In 1876, Lauth (8) heated p-phenylenediamine with sulfur; the hydrochloric acid solution of the reaction

- (5) Patterson, J. Am. Chem. Soc., 47, 540 (1925); 50, 3074 (1928).
- (6) Meyer and Jacobson, "Lehrbuch der organischen Chemie," Vol. 2, Part 3, (1920), p. 1490.
- (7) Bernthsen, Ann., 230, 77 (1885).
- (8) Lauth, Ber., 9, 1035 (1876).

product was treated with ferric chloride and a purple dye resulted. In the same year, Caro (9) applied Lauth's reaction to *p*-aminodimethylaniline and obtained a blue dye later known as methylene blue. Berntsen suspected that the phenothiazine nucleus was present in these two dyes. Previously, phenothiazine had not been reported so Berntsen set out to prepare it. Diphenylamine and sulfur were heated directly at 250-300°. Purification of the crude product by distillation and recrystallization gave about a 40% purified yield of product melting at 180-181°. Knoevenagel (10) later found that the addition of 1% iodine to the dry melt acted catalytically to lower the temperature and lessen the time necessary for completion of the reaction. He obtained a quantitative yield of crude material melting at 180°.

That an imino group was present in phenothiazine was demonstrated by Berntsen by the preparation of a methyl, ethyl, and acetyl derivative. Likewise, the presence of a sulfide linkage was proven by oxidation of 10-methylphenothiazine to a sulfone. The sulfide linkage was shown to be ortho to the imino group by the conversion of phenothiazine to phenyl-acridine by heating with benzoic acid and zinc chloride (11).

Berntsen (12) nitrated phenothiazine with fuming nitric

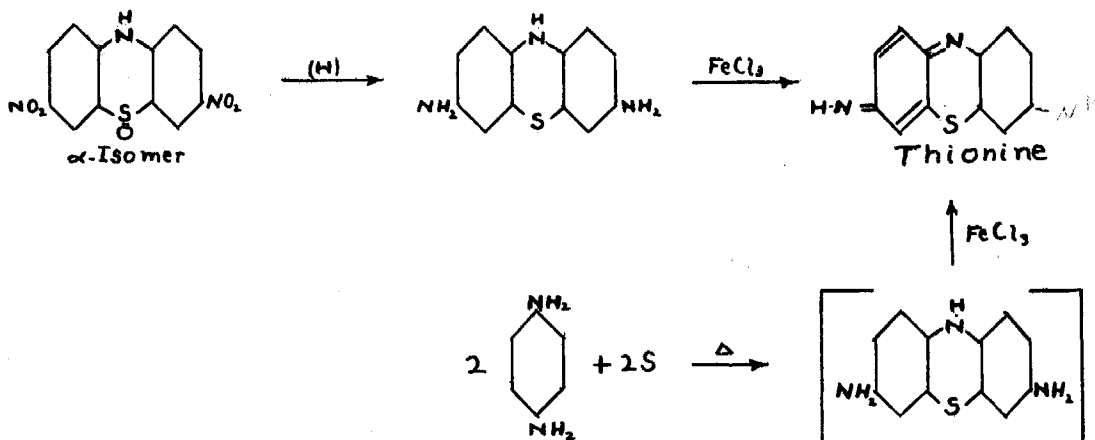
(9) Berntsen's obituary on Heinrich Caro, Ber., 45, 2012 (1912).

(10) Knoevenagel, J. prakt. Chem., (2), 89, 1 (1913).

(11) Berntsen, Ann., 230, 88, 93, 95, 100 (1885).

(12) Berntsen, Ann., 230, 116-133 (1885).

acid at 0° and obtained two dinitrophenothiazine sulfoxides, the so-called α - and β -isomers. The α -isomer was reduced to a diamino phenothiazine; oxidation of this diamine gave a dye identical with Lauth's violet, more commonly known as thionine.



The formation of thionine by these two series of reactions proves that a phenothiazine nucleus is present in thionine, and also that in α -dinitrophenothiazine, the nitro groups are para to the imino group. The structure of the β -isomer has never been proven.

Berntsen also obtained a mononitro-sulfoxide by more moderate conditions of nitration; reduction of this to an amine followed by oxidation with ferric chloride furnished a dye whose properties were so similar to those of the other dyes of the methylene blue series that it was considered to be a paraquinoid dye. Therefore, in the parent nitro-compound, it was concluded that the nitro group was in the 3-position (13).

(13) Berntsen, Ann., 230, 100-107 (1885).

Kehrmann and Zybs (14) nitrated 10-methylphenothiazine to give 3-nitro-10-methylphenothiazine sulfoxide and 3,7-dinitrophenothiazine sulfoxide. The structure was proven by showing the identity of these compounds with the methylated derivatives of Bernthsen's authentic 3-nitro- and 3,7-dinitrophenothiazine sulfoxides. Barnett and Smiles (15) reported a tetranitrosulfoxide which they believed to be 1,3,7,9-tetranitrophenothiazine sulfoxide. Kehrmann and Nossenko (16) were unable to repeat the English work. They did, however, obtain a trinitro-derivative which they believed to be 1,3,7-trinitrophenothiazine sulfoxide.

Phenothiazine is very sensitive to oxidizing agents as ferric chloride, a dark green solution and an iron-containing precipitate being formed (17). Hydrogen peroxide in alcohol oxidizes phenothiazine to the sulfoxide which acts as a base in the presence of mineral acids to give a series of phenazothionium salts. 10-Methylphenothiazine also yields sulfonium salts on oxidation in acid media (18).

Direct chlorination of phenothiazine, according to Unger and Hofmann (19) produces a very small yield of di- and tetrachlorophenothiazines, and some tetrachlorophenothiazine

- (14) Kehrmann and Zybs, Ber., 52B, 130 (1919).
- (15) Barnett and Smiles, J. Chem. Soc., 95, 1257 (1909).
- (16) Kehrmann and Nossenko, Ber., 46, 2809 (1913).
- (17) Bernthsen, Ann., 230, 83 (1885).
- (18) Smiles and co-workers, (a) J. Chem. Soc., 95, 1253 (1909);
(b) 97, 186 (1910); (c) 99, 145 (1911); (d) 101, 2294 (1912).
- (19) Unger and Hofmann, Ber., 29, 1362 (1896).

sulfoxide. The dichloro-derivative melting at 222° when nitrated, reduced, and treated with ferric chloride yielded no dye. From this it was concluded that the chlorine atoms must occupy positions para to the imino group. The tetrachloro-derivative melting at 235° was considered most probably to be 1,3,7,9-tetrachlorophenothiazine. Unger and Hofmann also chanced upon the fact that chlorination occurs when an ether-hydrogen chloride solution of phenothiazine is treated with nitrogen tetroxide and then heated, a mixture of mono-, di-, and tetrachlorophenothiazine, being formed. The tetrachloro-compound could be separated from the mono- and di-compounds and was found to be identical with that produced by direct chlorination. The dichloro-derivative was separated from the monochloro-derivative, but the German authors were unable to obtain the monochloro-derivative in a pure state. This dichloro-derivative melting at 225-227° was found to be isomeric with the direct chlorination dichloro-derivative; and on the basis of the behavior of its dinitro-derivative, it was considered to be 1,3-dichlorophenothiazine.

Page and Smiles (20) further investigated this method of chlorinating phenothiazine with hydrogen chloride and nitrogen tetroxide. They have shown that this reaction takes place through rearrangement of the phenazothionium salt. Apparently, nitrogen tetroxide oxidizes the sulfide group to the sulfoxide;

(20) Page and Smiles, J. Chem. Soc., 97, 1112 (1910).

and in the presence of hydrogen chloride, the phenazothionium chloride is formed. On heating, hydrogen chloride causes reduction, and rearrangement of the chlorine atom from the sulfur atom to the nucleus occurs. To demonstrate this hypothesis, the English authors treated phenothiazine sulfoxide with hydrochloric acid to obtain the sulfonium chloride. When this acid solution was warmed, Unger and Hofmann's mono- and dichloro-mixture was obtained in 70% yield. While Unger and Hofmann were not able to isolate the monochloro-compound, Page and Smiles proved conclusively that it was present in the mixture by nitration and isolation of a monochlorodinitro-sulfoxide. The position of the chlorine atom in monochloro-phenothiazine has never been determined. This rearrangement-halogenation does not go with hydrogen iodide, but does with hydrogen bromide giving a small yield of a monobromo-compound which could not be obtained pure. With 10-methylphenothiazine sulfoxide, this method of halogenation yields all monochloro-10-methyl-phenothiazine and none of the dichloro-derivative. Direct halogenation of 10-alkylphenothiazines has not been reported. Kehrmann and Nossenko (16) synthesized the previously unknown 3-nitrophenothiazine by warming Bernthsen's 3-nitro-sulfoxide (13) with alcoholic sulfuric acid. Also, 3-nitro-phenothiazine sulfoxide on treatment of a glacial acetic acid solution with hydrogen chloride yielded chloro-3-nitro-phenothiazine, with the chlorine atom probably in the 7-position.

Finzi (21) has shown that 10-methyl- and 10-ethylphenothiazines mercurate with ease when refluxed with an alcohol solution of mercuric acetate to yield a mixture of 3-acetoxymercuri- and 3,7-diacetoxymercuri-10-alkylphenothiazines. The corresponding phenyl and benzyl derivatives do not mercurate but are oxidized. The mono- and dimercurials of 10-alkylphenothiazines are readily separated by the solubility of the former in hot alcohol. The acetoxymercuri groups, converted to the chloromercuri groups, are replaceable by bromine and iodine in the usual manner. The structure of the 3,7-diacetoxymercuri-10-methylphenothiazine was proved by the replacement of the acetoxymercuri groups by nitro groups. The dimercurial was heated a few minutes with concentrated nitric acid; this treatment furnished a dinitro-sulfoxide identical with Kehrman's authentic 3,7-dinitro-10-methyl sulfoxide (14). Since the monomercurial could be further mercurated to the 3,7-dimercurial, it was evident that the monomercurial must contain its acetoxymercuri- group in the 3-position. By analogy, the 10-ethyl-derivatives were considered to mercurate in the same positions as the 10-methyl-derivatives.

Cleavage in the presence of mineral acids is a general reaction of mercurials. Finzi's method of proving structure, then, is open to the objection that instead of direct replacement, cleavage might occur followed by nitration of the

(21) Finzi, Gazz. chim. ital., 62, 175 (1932); C. A., 26, 4338 (1932)7.

demercurated nucleus not necessarily in the same positions originally occupied by the mercuri groups. Finzi does not mention this objection but seems to have been aware of it for he cites the work of Sachs and Ott (22) who were confronted with the same difficulty in the replacement of the mercuri group in 4-acetoxymercuridiphenyl sulfide, obtained by mercuration of diphenyl sulfide. In order to determine that the reaction did not proceed by demercuration and subsequent nitration, they treated diphenyl sulfide with nitric acid in the presence of mercuric acetate. Nitration occurred, to be sure, but the nitro-sulfoxide obtained was different from that obtained by treating the mercurial with nitric acid. Additional evidence in defense of straightforward replacement was furnished by Hanke (23) who treated o-chlorophenylmercuric acetate with concentrated nitric acid at 65° for ten minutes; he obtained only o-chloronitrobenzene. Hanke further stated that if the reaction were one of demercuration and subsequent nitration, a mixture of ortho-, and para-chloronitrobenzene should be obtained. No such mixture was found.

Finzi (21) also attempted to link his 3-iodo-10-methylphenothiazine with Kehrman's 3-amino-10-methylphenothiazine, but a Sandmeyer reaction of the latter compound could not be accomplished.

(22) Sachs and Ott, Ber., 59, 173 (1926).

(23) Hanke, J. Am. Chem. Soc., 45, 1324 (1923).

Friedel-Crafts acylation of phenothiazine has been reported by Scholl and Seer (24) who treated phenothiazine with phthalic anhydride in the presence of aluminum chloride in carbon disulfide solution. They obtained a very small yield of phenothiazine diphthaloylic acid. They did not prove the structure of this di-acid, but assigned the phthaloyl groups to positions 3 and 7 by analogy with nitration of phenothiazine. 10-Methylphenothiazine likewise gave a diphthaloylic acid. M.R. McCorkle, in this laboratory, treated phenothiazine with stearoyl chloride in the presence of aluminum chloride in carbon disulfide solution. He obtained two ketonic products, one melting at 78-79°, and the other at 125-135°. The former was regarded as the monostearoyl compound and the latter as the di-derivative. Neither compound has yet been analyzed.

A degradation of phenothiazine that might be of value in proof of structure work is that of Goske (25) who heated phenothiazine and freshly reduced copper under reflux in an atmosphere of illuminating gas to give a 60% yield of carbazole. Under the same conditions, 10-methylphenothiazine yields not 5-methylcarbazole, but carbazole itself (26).

Several typical examples of ring closure syntheses of phenothiazine derivatives will now be considered. 1-Nitrophenothiazine (the only 1-monosubstituted derivative to be reported)

(24) Scholl and Seer, Ber., 44, 1241 (1911).

(25) Holzmann, Ber., 21, 2069 (1888).

(26) Ullmann, Ann., 366, 97 (1909).

was prepared by Kehrmann and Nossenko (16) by refluxing 2,2'-diaminodiphenyl disulfide (1 mole) with 2,6-dinitrochlorobenzene (2 moles) and sodium acetate (2 moles) in alcohol solution for twenty four hours. The condensation product was treated with sodium sulfide solution to give a very poor yield of 1-nitrophenothiazine melting at 111°. The only phenothiazine carboxylic acid to be reported is 1-nitro-3-carboxyphenothiazine which Ullmann (27) prepared by condensing 4-chloro-3,5-dinitrobenzoic acid with *o*-aminothiophenol, and heating the condensation product with dilute sodium hydroxide. The yield of acid melting at about 316° was not reported.

(27) Ullmann, Ann., 366, 97 (1909).

DISCUSSION OF RESULTS

The phenothiazine used in these experiments was prepared by the dry melt method of Knoevenagel (10) and also using o-dichlorobenzene as a solvent. For preparing pure phenothiazine, the use of a solvent was found advantageous; but for the purpose of ethylation, the crude material prepared by the dry melt method was found satisfactory.

Metalation of 10-ethylphenothiazine with n-butyl-lithium and subsequent carbonation furnished an acidic gum in 36.6% yield, and 59% of the starting 10-ethylphenothiazine unchanged. Repeated extraction of this gum gave a solid acid (16% yield) melting at 156-165°. Further recrystallization of this acid, denoted for convenience as the "metalation acid", resulted in a constant melting point of 178-179°. Analysis of the metalation acid and its methyl ester showed it to be a monocarboxy acid of 10-ethylphenothiazine. There was no evidence of dimetalation.

Dibenzofuran undergoes n-butyl-lithium metalation with ease, only a six hour reflux period being necessary. On carbonation of the lithium compound, the writer and P.T. Parker, in this laboratory, have attained yields as high as 50% of crude 4-carboxydibenzofuran. Mercuration of dibenzofuran, however, goes with difficulty, the dry melt method being necessary (1). In comparison with dibenzofuran, 10-ethylphenothiazine undergoes n-butyl-lithium metalation with difficulty,

a twenty hour reflux period followed by carbonation furnishing only 36.6% of very crude acid. Mercuration of 10-ethylphenothiazine, however, goes with ease, taking place even in boiling alcohol solution.

As to the position taken by the lithium atom in metalation of 10-ethylphenothiazine, positions 1,2,3, and 4 are all possibilities. The most probable positions, however, are 1 and 3. 3-Metalation is a probability because mercuration (21) and nitration (14) both involve the 3-position. 1-Metalation is a probability because 5-ethylcarbazole has been shown to metalate ortho to the tertiary nitrogen atom (3).

The possibility of 3-metalation was excluded by the preparation of 3-carboxy-10-ethylphenothiazine from Finzi's 3-acetoxymercuri-10-ethylphenothiazine. The 3-acid was found to melt at 197.5-198.5°, thus dissimilar from the metalation acid.

Several unsuccessful attempts to synthesize 1-carboxy-10-ethylphenothiazine by ring closure were made.

It is the opinion of the writer, based on analogy with the metalation of 5-ethylcarbazole ortho to the tertiary nitrogen atom (3), that 10-ethylphenothiazine also metalates ortho to the nitrogen atom, or in the 1-position.

EXPERIMENTAL

Preparation of Phenothiazine.

Phenothiazine was prepared in one run in accordance with the directions furnished by L.E. Smith in a private communication. Eighty five grams (0.503 mole) of diphenylamine, 32 g. (1 g. atom) of sulfur, 0.85 g. of iodine (1% of the diphenylamine employed) and 100 cc. of *o*-dichlorobenzene were placed in a 300 cc. Erlenmeyer flask fitted with an air condenser and heated in an oil bath at 175° for about fifteen minutes until there was no more evolution of hydrogen sulfide. The reaction mixture was cooled in an ice bath and the resulting solid filtered and washed three times with small portions of ice-cold alcohol. The washed product was then recrystallized from about 600 cc. of toluene, using norite for decolorization. The yield of yellow crystalline material melting at 178-179° was 60 g. or 60%. Another recrystallization from toluene raised the melting point to 180-181°.

The use of a solvent was found convenient in the preparation of pure phenothiazine, but for the purpose of ethylation the crude product made by the dry melt method of Knoevenagel (10) was found satisfactory. A run of the same size as above was made omitting the solvent. The temperature was raised to 188-190°; after fifteen minutes of heating, evolution of hydrogen sulfide ceased. The melt was poured into a large evaporating dish and ground to a gray powder. The yield of crude product

was quantitative.

Preparation of 10-Ethylphenothiazine.

Phenothiazine was ethylated according to the method of Bernthsen (11). One hundred grams (0.5 mole) of crude phenothiazine, 200 cc. of absolute alcohol, and 80 g. (0.75 mole) of ethyl bromide were placed in a steel bomb (27a) of about one-liter capacity and heated at 120-130° for fifteen hours. On opening the bomb, the oily contents soon solidified. The filtered solid was washed with a small amount of cold alcohol, then dissolved in 1500 cc. of hot alcohol, decolorized with norite, and filtered hot. 10-Ethylphenothiazine separated out in long white prisms melting at 101-103°. The yield was 65 g. or 56%

In another run starting with one mole of crude phenothiazine, 175 g. of crude ethylated derivative was obtained. This was distilled at 176-179°/ 4mm. to give 150 g., a 66% yield, of white crystalline material melting at 92-101°.

The method of Stevens and Tucker (28) for alkylating carbazole with methyl and ethyl sulfate was employed in an attempt to ethylate phenothiazine, but negative results were obtained. R. L. Bebb, in this laboratory, was also unable to ethylate phenoxazine with ethyl sulfate.

(27a) The writer wishes to acknowledge his thanks to Dr. F.E. Brown for the use of his steel bomb and helpful advice in its operation.

(28) Stevens and Tucker, J. Chem. Soc., 123, 2145 (1923).

Metalation of 10-Ethylphenothiazine.

Six-hundredths of a mole of n-butyl-lithium was prepared by reacting in the customary manner 13.7 g. (0.1 mole) of n-butyl bromide in 175 cc. of ether with 1.52 g. (0.22 g. atom) of metallic lithium. The n-butyl-lithium solution was filtered through glass wool under dry nitrogen into a solution of 13.62 g. (0.06 mole) of 10-ethylphenothiazine dissolved in 100 cc. of anhydrous ether. The solution was refluxed with stirring for twenty hours. During the first few hours, a little gas was observed to escape from the mercury trap. Carbonation was effected by pouring the solution into an excess of solid carbon dioxide. The ether was distilled off and the dry residue was extracted with several portions of hot water. The filtered aqueous solution, on cooling, was acidified with dilute hydrochloric acid. The odor of valeric acid was apparent, indicating the presence of an excess of n-butyl-lithium. There also appeared, instead of a solid acid a brownish viscous gum. The amount of this gum, pressed between filter papers but probably not entirely water-free, was 6 g., and if considered a monocarboxy-acid, represented a yield of 36.6%. The gummy acid was soluble in benzene, toluene, chloroform, and alcohol, but insoluble in hot water and petroleum ether (b.p. 60-68°). The gum was also entirely soluble in dilute sodium carbonate, forming a red solution. On acidification with acetic acid, it was reprecipitated as a tarry substance. Eight grams, or 59% of the starting 10-ethylphenothiazine was recovered unchanged.

The gummy acid was extracted by refluxing with three successive portions of a mixture of 50 cc. of petroleum ether (b.p. 60-68°) and 10 cc. of toluene. This treatment left a solid residue of 2.6 g., a 16% yield, melting at 156-165°. Recrystallization from a 1:1 solution of chloroform and petroleum ether (b.p. 60-68°) yielded 0.95 g., a 6% yield, of yellow prisms melting at 173-175°. Further recrystallization from dilute alcohol gave fine yellow crystals melting at 178-179°. This melting point remained the same after a recrystallization from 1:1 chloroform-petroleum ether (b.p. 60-68°) followed by one from dilute alcohol. This acid is soluble in concentrated hydrochloric acid, as is also 10-ethylphenothiazine.

For monocarboxy-10-ethylphenothiazine, theory requires a neutralization equivalent of 271.2; the found value was 273.

Anal. Calcd. for $C_{15}H_{13}O_2NS$: N, 5.17. Found: N, 5.37 and 5.23.

This acid does not crystallize readily, even when pure. In recovering the sample of acid used in the determination of the neutralization equivalent, acidification with hydrochloric acid brought down the acid as a viscous oil. However, on standing over-night, the oil turned to a solid which melted normally at 178-179°.

The structure of this acid was not proven. However, the possibility of the carboxyl group being in the 3-position was excluded by the preparation of 3-carboxy-10-ethylphenothiazine, described later, which was found to melt at 197.5-198.5°.

Esterfication of Carboxy-10-ethylphenothiazine.

Seven-tenths of a gram (0.0026 mole) of the above carboxy-10-ethylphenothiazine was treated with an excess of diazomethane in ether solution. On removal of the ether, a yellow oil remained; this oil was dissolved in hot methyl alcohol and water was added dropwise to incipient turbidity. On cooling, 0.42 g., a 57% yield, of light yellow prisms melting at 111-112° was obtained. This melting point remained constant after another recrystallization from dilute methyl alcohol followed by one from petroleum ether (b.p. 60-68°).

Anal. Calcd. for $C_{12}H_{12}O_2NS$: C, 67.32; H, 5.30; N, 4.91.
Found: C, 66.87; H, 5.20; N, 5.05 and 5.06.

Preparation of 3-Acetoxymercuri-10-ethylphenothiazine.

10-Ethylphenothiazine was mercurated in accordance with the directions of Finzi (21). Twenty two and seven-tenths grams (0.1 mole) of 10-ethylphenothiazine was dissolved in 400 cc. of warm alcohol. To this was added a filtered solution of 50 g. (0.16 mole) of mercuric acetate in 450 cc. of alcohol and 10 cc. of glacial acetic acid. The solution was refluxed gently for three and one-half hours. A deep wine color was developed and much dimercurial separated out in the course of the reaction. The solution was filtered hot from 17 g. of the dimercurial and allowed to stand in the ice box for twelve hours. The rose colored precipitate that was obtained on filtration was washed well with water, then dissolved in 450 cc. of hot alcohol. The

solution was filtered hot from a small amount of green insoluble residue. After decolorization with norite, the solution was again filtered hot. On standing in the ice box, the monomercurial separated out as a practically white crystalline solid melting at 146-149°. The yield was 18.2 g., or 37%. Two recrystallizations from alcohol gave white platelets melting at 151-153°. Finzi (21) reports a melting point of 153°. Further recrystallization of a small amount of the 151-153° melting material lowered the melting point to 146-150°. It was found advisable to preheat the solvent before dissolving.

Preparation of 3-Iodo-10-ethylphenothiazine.

3-Iodo-10-ethylphenothiazine was prepared in a manner similar to that employed by Finzi (21) in the preparation of the corresponding methyl derivative. The chloromercuri compound of 3-acetoxymethyl-10-ethylphenothiazine was prepared by suspending 4.5 g. (0.0094 mole) ^{of what?} in an excess of 10% sodium chloride solution. The suspension was allowed to stand on a water bath for several hours with stirring. The filtered solid was suspended in 25 cc. of a molar solution of potassium iodide and 50 cc. of carbon tetrachloride was added to form a bottom layer. Twenty cc. of a 0.05 molar solution of iodine in potassium iodide was added slowly dropwise, with stirring. The iodine was taken up gradually from the aqueous layer. When it was apparent that the bottom layer was taking up no more iodine, the excess iodine was removed by adding dilute sodium sulfite

solution. The solution was filtered away from a sludge of mercuric iodide, and the carbon tetrachloride layer washed with water, and dried over anhydrous sodium sulfate. The filtered solution was allowed to evaporate at room temperature. The residue consisted of pinkish white needles melting at 124-125.5°. The yield was 2.7 g. or 80%. Two recrystallizations from alcohol gave white needles melting constantly at 126-127°.

In an attempted Carius analysis, a two-tenths gram sample was heated with 2 cc. of fuming nitric acid for ten hours at 300°, but instead of complete decomposition taking place, crystals of a polynitro-compound were obtained. Neither could a good decomposition be secured in a Parr bomb, analyses 15% below the theoretical being obtained. The compound was finally analysed successfully by the method of Baubigny and Chavanne (29).

Anal. Calcd. for $C_{11}H_{11}NIS$: I, 35.95. Found: I, 36.39 and 36.23.

Preparation of 3-Carboxy-10-ethylphenothiazine.

The Grignard reagent of 3-iodo-10-ethylphenothiazine was prepared in the customary manner by reacting 3.53 g. (0.01 mole) of the iodide dissolved in a mixture of 30 cc. of anhydrous ether and 30 cc. of dry benzene, 0.5 g. of magnesium turnings, several drops of *n*-butylmagnesium bromide, and a crystal of iodine. After about twenty minutes of refluxing, the reaction started

(29) Meyer, Hans, "Analyse und Konstitutionsermittlung organischer Verbindungen", Julius Springer, 1931, p. 140.

and the color turned to a greenish brown. Refluxing over a hot plate was continued for one hour. On cooling, the solution was filtered through glass wool into an excess of solid carbon dioxide. After hydrolysis with 10% hydrochloric acid, the ether-benzene layer was washed with water, then extracted with 10% sodium hydroxide solution. The rather insoluble sodium salt immediately separated out but was dissolved on the addition of more water. The basic solution was heated to expel dissolved ether, and acidified with hydrochloric acid. The yield of acid, a yellow solid melting at 194-196°, was 2.08 g. or 76%. A recrystallization from dilute alcohol followed by one from chloroform yielded yellow plates melting at 197.5-198.5°.

Theory requires a neutralization equivalent of 271.2; the found value was 272.

Anal. Calcd. for $C_{12}H_{12}O_2NS$: N, 5.17. Found: N, 5.27 and 5.31.

Preparation of 2-Carboethoxydiphenylamine.

2-Carboethoxydiphenylamine was prepared in the hope of obtaining 1-carboethoxyphenothiazine by heating with sulfur.

2-Carboxydiphenylamine, melting at 182-183°, was prepared in 86% yield according to the procedure of Ullmann and Dieterle (30) by coupling *o*-chlorobenzoic acid with aniline in the presence of potassium carbonate and a granule of copper oxide.

In the attempted esterification of 2-carboxydiphenylamine, (30) Ullmann and Dieterle, Ann., 355, 322 (1907).

Schroeter and Bisleb (31) reported negative results. They tried the reaction of the silver salt with ethyl iodide and the absolute ethanol-hydrogen chloride method. Evidently, in the latter procedure, sufficient time was not allowed, for the writer, using a long period of refluxing, was successful.

Forty grams (0.188 mole) of 2-carboxydiphenylamine was dissolved in 200 cc. of absolute ethanol. The solution was saturated with hydrogen chloride and refluxed for two hours. The solution was cooled and again saturated. The reaction was allowed to stand fourteen hours then refluxed for an additional five hours with a slow stream of hydrogen chloride passing over the surface of the solution. The reaction mixture was poured on ice and an oil separated out. This oil was extracted with 10% sodium carbonate solution, then with saturated calcium chloride solution. After drying over anhydrous sodium sulfate, the ester was distilled at 184-187°/ 6mm. The yield of yellow oil was 33 g. or 80%; 5 g. of the starting acid was recovered unchanged. To show that esterification and no other reaction had taken place, a small amount of the oil was refluxed with alcoholic potassium hydroxide, diluted with water, and acidified with hydrochloric acid to give the starting acid melting at 181-183°.

Anal. Calcd. for $C_{15}H_{13}O_2N$: N, 5.81. Found: N, 6.07.

Attempted Ring Closure of 2-Carboxy- and 2-Carboethoxydiphenylamine.

(31) Schroeter and Bisleb, Ann., 367, 144 (1909).

Four and twenty six-hundredths grams (0.02 mole) of 2-carboxydiphenylamine, 1.28 g. (0.04 g. atom) of sulfur, and 0.04 g. of iodine were dissolved in 20 cc. of *o*-dichlorobenzene and heated under reflux at 180° for fifteen minutes. The acid is unstable under these conditions for carbon dioxide as well as hydrogen sulfide was evolved. On working up this run, 2.2 g. of the starting acid was recovered unchanged.

In the attempt with 2-carboethoxydiphenylamine, 4.92 g. (0.02 mole) of the ester and 1.28 g. (0.04 g. atom) of sulfur with no solvent were heated in a 50 cc. Erlenmeyer flask equipped with an air condenser. The temperature of the metal bath was maintained at 285-300°. Hydrogen sulfide was evolved slowly at first, then the odor of ethyl mercaptan in the escaping gas became very apparent. Heating was discontinued after two hours when the evolution of gas had ceased. The dark colored tarry residue was extracted with ether, the ether removed, and the residue distilled. One and one-half grams of forerun distilling at 164-168° / 4 mm. was found to be the starting ester. A tailrun of 0.2 g. distilling at 168-240° / 4 mm. was dissolved in warm petroleum ether (b.p. 60-68°); on cooling, yellow needles of phenothiazine melting at 178-180° separated out. No phenothiazine-ester was found.

What happens, apparently, is that some of the ester is pyrolyzed to form a reducing agent for the sulfur. The ester, then, is cleaved by the hydrogen sulfide thus generated to yield

ethyl mercaptan and the free acid. The free acid under these conditions decarboxylates to yield diphenylamine which, in turn, undergoes normal ring closure with the unchanged sulfur.

Attempted Coupling of 2-Bromo-3-nitrobenzoic Acid and 2,2'-Diaminodiphenyl Disulfide.

An attempt was made to prepare 1-carboxyphenothiazine by a method analogous to that used by Kehrmann and Nossenko (16) in the synthesis of 1-nitrophenothiazine. As starting materials, 2-bromo-3-nitrobenzoic acid was prepared according to the Organic Syntheses procedure (32), and 2,2'-diaminodiphenyl disulfide was prepared in accordance with the directions of Teppema and Sebrell (33) by the sodium hydrosulfite reduction of 2,2'-dinitrodiphenyl disulfide.

In the attempted coupling, 0.47 g. (0.0019 mole) of the diamine, 0.92 g. (0.0019 mole) of 2-bromo-3-nitrobenzoic acid, and 0.51 g. (0.0038 mole) of sodium acetate were dissolved in 12 cc. of alcohol and refluxed for twenty four hours. Coupling did not take place as both starting materials were recovered unchanged.

In another attempt, a modification suggested by Ullmann's preparation of 2,2'-dicarboxydiphenylamine (34) was used. Sixty-two-hundredths of a gram (0.0025 mole) of the diamine, 1.42 g.

(32) Culhane, Organic Syntheses, Coll. Vol. I, 120 (1932).

(33) Teppema and Sebrell, J. Am. Chem. Soc., 49, 1751 (1927).

(34) Ullmann and Hoz, Ann., 355, 352 (1907).

(0.005 mole) of potassium o-chlorobenzoate, 0.82 g. (0.006 mole) of sodium acetate, 30 cc. of amyl alcohol, and a trace of copper bronze were refluxed for two hours. The amyl alcohol was removed by steam distillation; on working up the residue, the starting materials were recovered unchanged.

SUMMARY

- I. Mercuration of 10-ethylphenothiazine has been found to go with ease, but n-butyl-lithium metalation with difficulty.
- II. Authentic 3-carboxy-10-ethylphenothiazine has been prepared.
- III. A monocarboxy-acid has been obtained by carbonation of the lithium compound of 10-ethylphenothiazine. The position of the carboxyl group has not been determined, but the possibility of the 3-position being involved has been eliminated.
- IV. Several unsuccessful ring closure attempts have been described.