1954

Some synthetic studies with dibenzofuran

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NOTE TO USERS

SOME SYNTHETIC STUDIES WITH DIBENZOFURAN

by

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A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of
The Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

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Signature was redacted for privacy.

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Iowa State College
1954

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INTRODUCTION

Dibenzofuran was identified as such for the first time in 1870[1], but the study of this heterocycle and its derivatives did not commence in earnest until the first decade of the present century.[2,3]

The pace of this research increased considerably during the next 25 years and reached its peak in the years 1935-1940. Much of the published material of that period originated in this laboratory.[4-15]

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[1]W. Hoffmeister, Ber., 3, 747 (1870).

[2]W. Honigschmidt, Monatsh., 22, 561 (1901).

[3]W. Borsche and W. Bothe, Ber., 41, 1940 (1908).

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

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

[6]W. G. Bywater, Doctoral Dissertation, Iowa State College, 1934.

[7]W. H. Kirkpatrick, Doctoral Dissertation, Iowa State College, 1935.

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

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

[10]E. W. Smith, Doctoral Dissertation, Iowa State College, 1936.

[11]C. W. Bradley, Doctoral Dissertation, Iowa State College, 1937.

[12]P. T. Parker, Doctoral Dissertation, Iowa State College, 1937.

During World War II and the years immediately following, the amount of published material lessened, but several years ago the volume began to increase once more, a trend which is continuing.

These fluctuations appear to be readily explicable on the basis of, respectively, increasing interest in an undeveloped field, the channeling of research effort into other fields during the war, together with decreased graduate enrollment in chemistry and a reawakening of interest in dibenzofuran, especially from the standpoint of industrial applications. In recent years it has been found that the dibenzofuran nucleus can be incorporated advantageously into molecules suitable for use as dyes, pharmaceuticals, polymers and insecticides.

The investigations described in this dissertation were stimulated by an interest in the biological import of various dibenzofuran derivatives, especially those modeled after related heterocyclic molecules.

A general picture of dibenzofuran chemistry can be obtained by consultation of Elderfield's Volume II.[16] For more

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

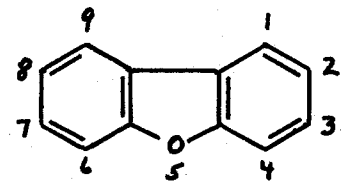
[14]J. Swislowsky, Doctoral Dissertation, Iowa State College, 1939.

[15]T. H. Cook, Doctoral Dissertation, Iowa State College, 1940.

[16]R. C. Elderfield, "Heterocyclic Compounds", John Wiley and Sons, Inc., New York, N.Y., 1951, Vol. II, Chap. 3.

detailed information one should examine the previously listed theses and dissertations from this laboratory as well as more recent ones.[17-23]

The numbering system (I) employed in this dissertation is that which was adopted by Chemical Abstracts in 1937.



I

Publications appearing in foreign journals usually make use of the system indicated by II. Also, these articles

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

[18]J. P. Thirtle, Doctoral Dissertation, Iowa State College, 1943.

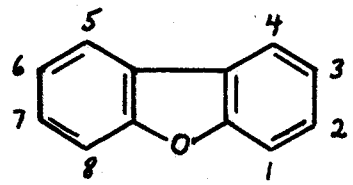
[19]S. Avakian, Doctoral Dissertation, Iowa State College, 1944.

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

[21]F. A. Yeoman, Doctoral Dissertation, Iowa State College, 1944.

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

[23]R. K. Ingham, Doctoral Dissertation, Iowa State College, 1952.



II

usually refer to the heterocycle as diphenylene oxide, biphenylene oxide, dibenzofurane or dibenzfuran.

In this dissertation the numbering of all dibenzofuran compounds has been adjusted to style I where necessary and where possible. When a foreign publication refers to a 2-substituted dibenzofuran, for example, it is assumed that this actually is a 3-substituted dibenzofuran according to system I, unless there is evidence to the contrary.

All dibenzofuran compounds are named in the general style which has been in use in this laboratory. Thus, 2-aminodibenzofuran is used in preference to 2-dibenzofuranamine. Condensed ring systems are named as derivatives of dibenzofuran whenever possible.

HISTORICAL

Some 20 years ago, research on dibenzofuran and its derivatives was commenced in this laboratory. Interest in this heterocycle was occasioned by the hope that its oxidation or that of its derivatives might yield furan-2,3,4,5-tetracarboxylic acid.[4] Such did not prove the case; however, the desired acid was synthesized by another method.

The study of dibenzofuran was continued though, because of the paucity of information available concerning its substitution reactions and orientation rules.

It was also observed that a structural similarity exists between dibenzofuran and a portion of the morphine molecule. This encouraged attempts to synthesize dibenzofuran derivatives possessing analgesic potency.

Later, the introduction of the dibenzofuran nucleus into compounds designed to be antimalarials and tuberculostats was undertaken. In addition, miscellaneous biological applications of dibenzofuran compounds have been proposed.

The following paragraphs contain an account of evaluations of dibenzofuran and its derivatives as physiological agents. No claim is made that all literature references are included. The Decennial Subject Indices of Chemical Abstracts do not always indicate that testing has been carried out with a particular compound, though such information may be indicated in the abstract. Also, the Subject Index for 1953 has not

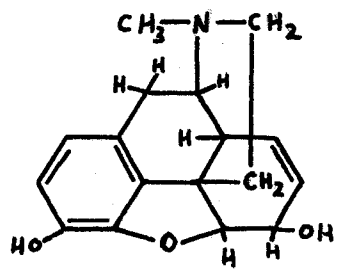
appeared at this date. Chemical Abstracts for 1953 and 1954 through Volume 48, No. 10 has been examined abstract by abstract in the sections pertinent to this study. The issues of the more important chemical journals for the past year have also been carefully checked.

In the main, however, published compilations of the results of the testing of organic compounds for various types of physiological activity have proven to be the most fruitful sources of such information.

Physiological Activity in the Dibenzofuran Series

Analgesic and anaesthetic activity

The preparation and testing of dibenzofuran compounds for analgesic and anaesthetic properties was inspired by the recognition of the resemblance of this heterocycle to a portion of the morphine molecule (III). An examination of the



III

structural formula for morphine indicates the presence of a partially reduced dibenzofuran nucleus as well as phenanthrene

and isoquinoline systems, also partially reduced.

Relatively early in dibenzofuran research, attempts were made to take advantage of this structural relationship. Mayer and Krieger[24] found that 2-(γ-aminopropyl)dibenzofuran and its heteronuclear reduction product, 1,2,3,4-tetrahydro-8-(γ-aminopropyl)dibenzofuran possessed no morphine-like action for warm blooded animals. In the same year von Braun[25] reported that aminohexahydrodibenzofuran and α-aminoethylhexahydrodibenzofuran were physiologically inactive.

Workers in this laboratory have approached in two ways the problem of achieving morphine-like action within the dibenzofuran series. Appropriate groups were attached to the dibenzofuran nucleus,[5,6,7,13,14] and attempts were made to prepare 1,9-disubstituted dibenzofurans and to bridge the 1 and 9 positions.[12,13,14,18,19,20,21] The story of the latter efforts is largely one of failure. Although 1,9-disubstituted dibenzofurans may have been obtained, there is no evidence at this time to indicate that these positions have been bridged.

The introduction of activating side chains proved fruitful in that compounds possessing some analgesic and anaesthetic activity were obtained.

Since the preparation of analgesics was not the subject of the writer's experimental work and since extensive tabulations

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[24]F. Mayer and W. Krieger, Ber., 55, 1659 (1922).

[25]J. von Braun, ibid., 55, 3761 (1922).

of the analgesic activity of dibenzofuran derivatives submitted from this laboratory have been compiled previously, no such listing is presented in this dissertation. Table 1 lists compounds not included in the previous listings.[7,12,13,14,15]

The experimental procedures for the preparation of the some 140 compounds submitted from this laboratory for testing as analgesics are distributed throughout the theses and dissertations on dibenzofuran which appeared during the years 1933-1944. Publication of these procedures has been primarily in the Journal of the American Chemical Society in a series of 24 consecutively-numbered papers.[26]

Publications from other laboratories relative to the synthesis and testing of dibenzofuran compounds for analgesic and anaesthetic properties are available in a reprint collection.[27]

Discussion here is confined chiefly to compounds for which no definite statements of activity are available.

The properties of certain amino alcohols derived from dibenzofuran and 1,2,3,4-tetrahydrodibenzofuran have been

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[26] H. Gilman, E. W. Smith and H. Oatfield, J. Am. Chem. Soc., 56, 1412 (1934), and succeeding papers.

[27] "Report of Committee on Drug Addiction 1929-1941 and Collected Reprints 1930-1941", National Research Council, Washington, D. C., 1941.

reported.[28,29] The compounds, which possess the side chain $-CHOH-CH_2-NR_2$, were prepared so as to permit a comparison with amino alcohols of the phenanthrene series. No pharmacological data for these compounds are presented in the papers; however, some of the compounds reported in the first of these two papers were also reported by Kirkpatrick and Parker,[30] and in their dissertations[7,12] may be found the results of the tests for analgesic activity.

The preparative details for a number of benzofuroquinolines (pyridodibenzofurans) have been published.[30,31] It has been reported[31] that for these compounds physiological activity increases progressively from the unhydrogenated benzofuroquinolines through the tetrahydro compounds to a maximum in the N-methyl tetrahydro compounds. No animals die with effective doses and analgesia, general depression, muscular disturbance, emesis and temperature depression are observed. The members of the [2,3-f] series were found to be slightly more active than those of the isomeric [3,2-g] series. The analgesic activities for some of these compounds are to be found in the dissertations of Kirkpatrick[7] and Parker.[12]

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[28] E. Mosettig and R. A. Robinson, J. Am. Chem. Soc., 57, 2186 (1935).

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

[30] W. H. Kirkpatrick and P. T. Parker, ibid., 57, 1123 (1935).

[31] E. Mosettig and R. A. Robinson, ibid., 57, 902 (1935).

Eddy[32] found that when the effects of identical side chains were compared, the dibenzofuran compounds had greater analgesic effect than the phenanthrene derivatives. This apparent advantage was counterbalanced, however, by the greater toxicity of the dibenzofuran compounds. The many compounds tested (on cats) include some reported by previously-cited investigators. Parker[12] has discussed Eddy's results rather thoroughly.

Burtner and Lehmann[33] also found dibenzofuran derivatives to be toxic. They tested a number of alkyl- and dialkylamino-alkyl esters of dibenzofurancarboxylic acids for local anaesthetic activity. Though β-diethylaminoethyl-2-dibenzofuran-carboxylate possessed a duration of anaesthesia comparable to that of procaine, it and other dibenzofuran derivatives were not considered to be of value as anaesthetics because of the irritating action on human skin and the pain incurred on injection. Table 1 includes the compounds tested.

A German[34] and a British[35] patent which appear to be duplications of each other list a number of derivatives of

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[32]N. B. Eddy, J. Pharmacol. Exptl. Therap., 58, 155 (1936).

[33]R. R. Burtner and G. Lehmann, J. Am. Chem. Soc., 62, 527 (1940).

[34]German Patent 550,327 [C. A., 26, 4062 (1932)].

[35]British Patent 373,624 [British C. A., B, 912 (1932)].

aminodibenzofurans which are variously said to have anaesthetic and therapeutic properties[34] and anaesthetic and amoebicidal properties.[35] The abstracts of these patents do not indicate that these compounds were examined for antimalarial effectiveness, as has been reported previously.[36]

The preparation of tri-4-dibenzofurylantimony and diphenyl-(2-dibenzofuryl)antimony was undertaken[37] because other dibenzofuran derivatives possessed analgesic properties. The results of pharmacological tests on these organo-metallics have not been published.

In a study of the toxicity, antipyretic activity and analgesic action of some carbazole and tetrahydrocarbazole compounds, Eagle and Carlson[38] included some compounds not of these series, among them, 2-acetamidodibenzofuran. They found this amide to be less toxic than aspirin while it possessed a slightly greater temperature lowering effect, a higher antipyretic index and greater antipyretic and analgesic activity. The rat was the test animal.

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

[37]G. J. O'Donnell, Doctoral Dissertation, Iowa State College, 1944.

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

Table 1

Analgesic and Anaesthetic Activity
of Some Dibenzofuran Compounds

Compound	Activity	Ref.
2-acetamidodibenzofuran	19[a]	(38)
3-amino-(β-diethylaminoethyl)-8-dibenzofurancarboxylate	---	(33)
β-n-amylaminoethyl-2-dibenzofurancarboxylate	27 + at 0.5%[b]	(33)
x-bromo-3-(β-diethylaminoethylamino)dibenzofuran	anaesthetic properties	(34,35)
2-(α-bromoethyl)dibenzofuran	analgesic activity	(39)
3-[β-(β'-diethylaminoethoxy)-ethylamino] dibenzofuran	anaesthetic properties	(34,35)
3-bis-[β-(β'-diethylaminoethoxy)-ethyl] aminodibenzofuran	anaesthetic properties	(34,35)
3-(β-diethylaminoethylamino)dibenzofuran	anaesthetic properties	(34,35)
3-bis-(β-diethylaminoethyl)aminodibenzofuran	anaesthetic properties	(34,35)
2,4-bis-(β-diethylaminoethylamino)-dibenzofuran	anaesthetic properties	(34,35)
3,7-bis-(β-diethylaminoethylamino)-dibenzofuran	anaesthetic properties	(34,35)
β-diethylaminoethyl-2-dibenzofuranacrylate	10 + at 0.5%[b] 13 + at 1.0%[b]	(33)

[a]Maximum average algesimetric value at 200 mg./kg. in gm.

[b]Duration of corneal anaesthesia in rabbits in minutes (0 = none, - = weak, + = full, ++ = deep) at conc. indicated.

Table 1 (concluded)

Compound	Activity	Ref.
β-diethylaminoethyl-2-dibenzofurancarboxylate	4 + at 0.1%[b] 11 ++ at 0.5%[b] 20 ++ at 1.0%[b]	(33)
β-diethylaminoethyl-3-dibenzofurancarboxylate	5 + at 0.1%[b] 25 ++ at 0.5%[b] 30 ++ at 1.0%[b]	(33)
β-diethylaminoethyl-4-dibenzofurancarboxylate	4 - at 0.1%[b] 11 + at 1.0%[b]	(33)
3-[β-(β'-diethylaminoethylthiol)ethylamino] dibenzofuran	anaesthetic properties	(34,35)
γ-diethylaminopropyl-2-dibenzofurancarboxylate	8 - at 0.1%[b] 14 + at 0.5%[b] 35 ++ at 1.0%[b]	(33)
2-[α-(β'-hydroxyethylaminoethyl)] dibenzofuran hydrochloride	analgesic activity	(39)
3-[α-hydroxy-β-(1-piperidyl)-propylamino] dibenzofuran	anaesthetic properties	(34,35)
β-isobutylaminoethyl-2-dibenzofurancarboxylate	0 at 0.1%[b] 14 + at 0.5%[b] 26 + at 1.0%[b]	(33)
2-[β-(1-piperidyl)ethyl] dibenzofuran hydrochloride	analgesic activity	(39)
3-[β-(1-piperidyl)ethylamino] dibenzofuran	anaesthetic properties	(34,35)
3-bis-[β-(1-piperidyl)ethylamino] dibenzofuran	anaesthetic properties	(34,35)

A recent British patent[39] claims that three dibenzofuran compounds, 2-[α-(β'-hydroxyethylaminoethyl)] dibenzofuran hydrochloride, 2-(α-bromoethyl)dibenzofuran and 2-[α-(1-piperidyl)ethyl] dibenzofuran hydrochloride show antispasmodic and analgesic activity.

Antimalarial activity

Since World War II there has been little, if any, effort made to discover antimalarial agents within the dibenzofuran series. Many of the dibenzofuran derivatives tested under the wartime research program[40] subsidized by the Office of Scientific Research and Development were examined as a part of a random screening process[41] rather than as a result of the feeling that this heterocyclic system was a potential source of antimalarials. Present day research in the field of antimalarials is concerned primarily with the synthesis and testing of heterocyclic nitrogen compounds, e.g., quinoline, acridine and pyrimidine derivatives.

Table 2 lists the dibenzofuran derivatives which have been tested for antimalarial effectiveness. Most of these

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[39]British Patent 687,892 [C. A., 48, 4594 (1954)].

[40]F. Y. Wiselogle, "Survey of Antimalarial Drugs 1941-1945", J. W. Edwards, Ann Arbor, Mich., 1946.

[41]R. C. Elderfield, Chem. and Eng. News, 24, 2598 (1946) reported that only about one-third of the 12,400 compounds examined for antimalarial activity were synthesized especially for that purpose.

compounds were located in Wiselogle's extensive compilation; several were found in a government publication.[42]

Over 100 compounds were supplied by this laboratory[43] to the government-sponsored testing program under terms of a contract which went into effect in the summer of 1944.

The preparation of 4,6-diaminodibenzofuran was undertaken[44] so that this compound might be tested for antimalarial activity, but there is no indication that this testing was done.

Martin[45] synthesized 2- and 3-fluorodibenzofuran and reported that these two compounds had been submitted for testing, but the results of these tests are unknown.

A number of compounds based on a pyridine ring fused to a dibenzofuran nucleus, i.e., benzofuroquinolines or pyridodibenzofurans, have been investigated.[46] Though activating

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[42]G. R. Coatney, W. C. Cooper, N. B. Eddy and J. Greenberg, "Survey of Antimalarial Agents", Public Health Monograph No. 9, Federal Security Agency, U. S. Govt. Printing Office, Washington, D. C., 1953.

[43]See H. Gilman, L. Tolman, F. Yeoman, L. A. Woods, D. A. Shirley and S. Avakian, J. Am. Chem. Soc., 68, 426 (1946) and H. Gilman and S. Avakian, ibid., 68, 580 (1946) for the preparation of some of these compounds.

[44]H. Gilman and S. Avakian, ibid., 67, 349 (1945).

[45]G. A. Martin, Jr., Doctoral Dissertation, Iowa State College, 1945.

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

Table 2

Antimalarial Activity of Dibenzofuran and Some Derivatives

Compound	Activity		Ref.
2-aminodibenzofuran	A-3	inactive	(40)
	1-A	Q = 30[a] (toxicity test)	
	MTD[b]	0.015 mg./g.	(42)
	FTD[c]	0.012 mg./g.	
	METD[d]	inactive	
	PT[e]	inactive	
3-aminodibenzofuran	D-1	Q < 0.15[a] at MTD[b]	(40)
	F-1	Q < 0.02[a]	
2-amino-3-acetamidodibenzofuran	F-1	Q < 0.06[a]	(40)
1-bromo-4(γ-diethylaminopropylamino)dibenzofuran	B-1	D < 0.06[f]	(40)
2-bromo-3(γ-diethylaminopropylamino)dibenzofuran	B-1	inactive	(40)
1-bromo-3(γ-diethylaminopropylamino)-4-methoxydibenzofuran	C-1	slightly active	(40)
2-cyanodibenzofuran	B-4	Q < 0.02[a]	(40)
3,7-diaminodibenzofuran	D-1	Q < 0.15[a] at MTD[b]	(40)
	F-1	Q < 0.10[a] at MTD[b]	

[a]Quinine equivalent.

[b]Maximum tolerated dose.

[c]Fully tolerated dose.

[d]Minimum effective therapeutic dose.

[e]Prophylactic test.

[f]Sulfadiazine equivalent.

Table 2 (continued)

Compound	Activity		Ref.
dibenzofuran	F-1	Q < 0.06[a] at MTD[b]	(40)
1-(4-dibenzofurylmethyl)-piperidine	B-4	Q < 0.08[a] at MTD[b]	(40)
2-[γ-(3-dibenzofuryl)propyl]-3-hydroxy-1,4-naphthoquinone	F-1	active	(40)
3-(γ-diethylaminopropylamino)-dibenzofuran	B-1	inactive	(40)
4-(γ-diethylaminopropylamino)-dibenzofuran	B-1 B-4	D < 0.10[f] Q < 0.03[a]	(40)
2,7-bis(γ-diethylaminopropyl-amino)dibenzofuran	B-1	toxic at 450 mg./kg.	(40)
2,8-bis(γ-diethylaminopropyl-amino)dibenzofuran	B-1	inactive at 110 mg./kg. daily	(40)
2-(γ-diethylaminopropylamino)-3-bromodibenzofuran	B-1	inactive	(40)
1-(γ-diethylaminopropylamino)-3,4-dimethoxydibenzofuran	C-1	inactive	(40)
3-(γ-diethylaminopropylamino)-6-iododibenzofuran	B-1	inactive	(40)
1-(γ-diethylaminopropylamino)-2-methoxydibenzofuran	C-1	inactive	(40)
1-(γ-diethylaminopropylamino)-4-methoxydibenzofuran	C-1	inactive	(40)
1-dimethylaminomethyl-2-hydroxydibenzofuran	B-4	Q < 0.06[a]	(40)
2-(β-dimethylaminopropionyl)-dibenzofuran hydrochloride	F-1	Q < 0.06[a]	(40)
1,2,3,4,4a,9b-hexahydrodibenzo-furan	F-1	Q < 0.02[a]	(40)

Table 2 (continued)

Compound	Activity		Ref.
2-(α-hydroxy-β-dimethylamino-ethyl)dibenzofuran hydrochloride	A-1 A-3 F-1	Q < 0.3[a] slightly active Q < 0.10[a]	(40)
	MTD[b] FTD[c] METD[d]	0.088 mg./g. 0.066 mg./g. inactive	(42)
3-(α-hydroxy-β-dimethylamino-ethyl)-6,7,8,9-tetrahydro-dibenzofuran hydrochloride	A-1 A-3	Q < 0.06[a] inactive	(40)
	MTD[b] FTD[c] METD[d] PT[e]	0.132 mg./g. 0.088 mg./g. inactive inactive	(42)
2-(α-hydroxy-β-dimethylamino-propyl)dibenzofuran hydrochloride	F-1	Q < 0.10[a]	(40)
2-[α-hydroxy-γ-(1-piperidyl)-propyl]dibenzofuran	F-1	Q < 0.10[a]	(40)
2-methoxy-3-(γ-diethylamino-propylamino)dibenzofuran	C-1	inactive	(40)
γ-(3-nitro-4-methoxy-1-diben-zofuran)butyric acid	B-4	Q < 0.06[a]	(40)
pyrido-[2,3-c]-5-aminodibenzo-furan	F-1	Q < 0.10[a]	(40)
pyrido-[3,2-b]-?-diethylamino-propylaminodibenzofuran		inactive	(46)
pyrido-[3,2-b]-?-[γ-(4-mor-pholinyl)propylamino]-dibenzofuran		inactive	(46)
pyrido-[3,2-b]-3-[γ-(4-mor-pholinyl)propylamino]-dibenzofuran	F-1	Q < 0.08[a]	(40)

Table 2 (concluded)

Compound		Activity	Ref.
pyrido-[2,3-c]-5-[γ-(4-morpholinyl)propylamino]-dibenzofuran	F-1	inactive	(40)
pyrido-[2,3-c]-5-nitrodibenzofuran	F-1	Q < 0.08[a]	(40)
1,2,3,4-tetrahydropyrido-[2,3-c]-dibenzofuran hydrochloride	A-3	slightly active	(40)
tri-4-(dibenzofuryl)arsine	B-4	Q < 0.015[a]	(40)
1-(m-trifluoromethylphenylazo)-2-hydroxydibenzofuran	B-4	Q < 0.15[a]	(40)
1-(m-trifluoromethylphenylazo)-2,8-dihydroxydibenzofuran	B-4	Q < 0.015[a]	(40)

groups were attached to the nuclei, these compounds were at best only very slightly active.

The antimalarial activities of the compounds in Table 2 are given in quinine and sulfadiazine equivalents.

> The quinine equivalent of an antimalarial drug is the ratio by weight of the dose of quinine to the dose of the drug under assay when both drugs, administered under identical conditions, produce the same response in parasitized birds.[47]

A variety of testing procedures was employed. Identification of the tests, e.g., B-4, is given in Wiselogle.

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[47]Wiselogle, op. cit., Vol. I, p. 62.

Of the 39 dibenzofuran compounds examined (Table 2), 25 showed some activity with one compound, 2-[γ-3-dibenzofuryl)-propyl]-3-hydroxy-1,4-naphthoquinone, being classed as active. In view of these results, it seems likely that by the introduction of proper substituents, significant antimalarial activity within the dibenzofuran series may yet be achieved.

Antituberculosis activity

4-Amino-2',2,4,5-tetrachlorodiphenyl ether has been found[48] to be inhibitory to Mycobacterium tuberculosis at a dilution of 1:1,000,000. Other chloro-aminodiphenyl ethers were less potent, e.g., 2,4-dichloro-4-aminodiphenyl ether (1:600,000), 2-chloro-4'-aminodiphenyl ether (1:150,000), 4-chloro-4'-aminodiphenyl ether (1:110,000) and 4-chloro-2'-aminodiphenyl ether (1:15,000).

Dibenzofuran may be regarded as a "closed model" of diphenyl ether; hence, it is not surprising that corresponding activities in these two series are observed.

An additional compound of potential value, 2,8-dibromo-3-aminodibenzofuran, has been synthesized,[49] but pharmacological data on it are not yet available. The same paper indirectly suggests that 2-bromo-8-aminodibenzofuran is worthy of being

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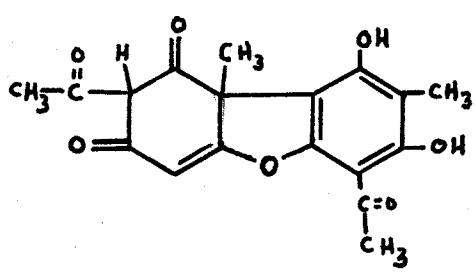
[48] V. C. Barry, L. O'Rourke and D. Twomey, Nature, 160, 800 (1947).

[49] H. Gilman and R. K. Ingham, J. Am. Chem. Soc., 75, 4843 (1953).

tested for antituberculosis activity. The activity of this compound should approximate that of 4-chloro-4'-aminodiphenyl ether, if dibenzofuran and diphenyl ether are always as closely related in their physiological manifestations as in their structures.

Among the compounds tested by Barry and co-workers[48] was usnic acid. This naturally occurring substance inhibited strongly (1:500,000) the growth of the tubercle bacillus *in vitro*; in addition, the activity was retained to a great extent in the presence of 5% human serum.

Usnic acid has been the subject of a great deal of study, both as to its chemical constitution and its antibacterial activity. (The discovery of the antibacterial properties of lichen extracts[50] led to the isolation of individual lichen acids, usnic acid included.) The accepted structure is one



Usnic Acid

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[50]For a general review on this subject, the reader should consult F. Bustinza, Endeavour, 10, 95 (1951).

proposed by Robertson and co-workers.[51,52] The relationship to a highly substituted dibenzofuran is evident. Apparently there is no biological specificity associated with the configuration at the asymmetric center in the molecule, for d-usnic acid and l-usnic acid (as free acids or sodium salts) possess equal inhibitory potency for avian tubercle bacilli.[53,54]

There is, however, a high degree of specificity of the entire usnic acid molecule.[55,56] Acetylation of the two phenolic hydroxyl groups diminishes the activity of d-usnic acid by 75 per cent. Strangely enough, l-diacetylusnic acid is reported to retain one-half of the activity (1:80,000) of the original acid. Likewise, reduction of the acyclic double bond renders the acid less active.

A number of highly substituted dibenzofuran compounds resembling usnic acid and didymic acid (IV), another metabolic

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[51] F. H. Curd and A. Robertson, J. Chem. Soc., 894 (1937).

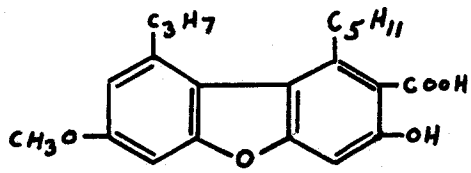
[52] R. T. Foster, A. Robertson and T. V. Healy, ibid., 1594 (1939).

[53] S. Shibata, T. Ukita, Y. Miura and T. Tamura, J. Penicillin (Japan), 1, 588 (1948) [C. A., 43, 6697 (1949)].

[54] A. Marshak, W. B. Schaefer and S. Rajagopalan, Proc. Soc. Exptl. Biol. Med., 70, 565 (1949).

[55] S. Shibata, Y. Miura, C. Ukita and T. Tamura, J. Pharm. Soc. Japan, 68, 298 (1948) [C. A., 45, 6691 (1951)].

[56] S. Shibata, ibid., 64, 50 (1944) [C. A., 45, 2929 (1951)].



IV

product of lichens, has been synthesized and tested[57,58] (see Table 3) for antibacterial activity. Of these compounds, decarbo-nor-didymic acid (1-n-propyl-3,7-dihydroxy-9-n-amyl-dibenzofuran) proved to be the most effective as a tuberculostatic agent, being inhibitory at a dilution of 1:320,000.

Clinical use of usnic acid for treatment of tuberculosis has been reported,[59] but there is no indication in the literature that the dibenzofuran derivatives have been so employed.

Another study of diphenyl ether derivatives was undertaken by Tomita and Watanabe.[60] 2-Aminodiphenyl ether hydrochloride, the only amine tested, was effective against the human strain

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[57] S. Shibata, Y. Miura, H. Sugimura and Y. Toyoizumi, ibid., 68, 303 (1948) [C. A., 45, 6692 (1951)].

[58] M. Naito, A. Shihoda, M. Ohta, F. Fujikawa, K. Nakazima, H. Fujii, A. Tokuoka and Y. Hitosa, ibid., 72, 1047 (1952) [C. A., 46, 10286 (1952)].

[59] R. Patiala, J. Patiala, S. Siitola and P. Heilala, Suomen Kemistilehti, 21A, 217 (1948) [C.A., 43, 9267 (1949)].

[60] M. Tomita and W. Watanabe, J. Pharm. Soc. Japan, 71, 1198 (1951) [C. A., 46, 7618 (1952)].

of *M. tuberculosis* at a dilution of 1:4,000. (Barry, *et. al.*,[48] found 1:35,000.) The sole dibenzofuran derivative examined, 3-isocaproyldibenzofuran, was inhibitory at < 1:70,000. A somewhat lower value (< 1:50,000) was reported for a related compound, 4-isocaproyldiphenyl ether. None of the diphenyl ethers possessed any remarkable growth inhibition against tubercle bacilli.

Because of previous findings which indicated that aromatic amines in which the amino group is *para* to a lipophilic group are effective tuberculostats, a number of aminodibenzofurans were tested. Using the human strain of *M. tuberculosis*, Doub and Youmans[61] established that the order of effectiveness of substitution relative to the ether linkage is *para* > *meta* > *ortho*. Examining Table 3, it is apparent that 2-aminodibenzofuran which may be considered *para*-substituted is as effective as any of the dibenzofuran compounds tested. This compound was considered worthy of evaluation by means of *in vivo* test in the mouse, but it proved ineffective. (2-Aminodibenzothiophene showed some suppressive effect but too little to be of practical significance.) The high chronic toxicity of the compounds tested by Doub and Youmans coupled with the marked loss of potency in the presence of serum negates the attractive *in vitro* values in absence of serum.

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

Nicotinamide is active only at a 1:500 dilution without serum and <1:125 in the presence of 10% serum.[62] Nicotinamidine also is active only at high concentrations, 1:125 and <1:125, respectively. The introduction of aromatic nuclei or the dibenzofuran nucleus into the side chains of these compounds results in a great increase in activity. However, even the highest activity observed, N-(p-phenoxyphenyl)-nicotinamide (1:16,000 and 1:32,000), is not outstanding. N-(3-Dibenzofuryl)nicotinamide was active at <1:8,000 and N-(3-dibenzofuryl)nicotinamidine at <1:2,000 in the presence or absence of serum.

The results of the in vitro testing of various dibenzofuran compounds for antituberculosis activity are presented in Table 3. Most of the information contained therein was obtained from a review[63] compiled by the Chemical-Biological Coordination Center of the National Research Council. The majority of the dibenzofuran compounds listed were prepared and supplied by this laboratory.

A discussion of the activities of antituberculosis compounds in general is available in the dissertation of Ingham.[23]

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[62] J. N. Baxter and J. Cymerman, J. Chem. Soc., 1490 (1953).

[63] G. P. Youmans, L. Doub and A. S. Youmans, "The Bacteriostatic Activity of 3500 Organic Compounds for Mycobacterium Tuberculosis Var. Hominis", Review No. 4, National Research Council, Washington, D. C., 1953.

Table 3

In Vitro Antituberculosis Activity of Dibenzofuran and Some Derivatives

Compound	Bacteriostatic concentration			Ref.
	Mg. %[a]	Mg. %[a] (serum)	Highest inhibiting dilution	
1-acetamido-3,4-dihydroxydibenzofuran	10.0	10.0[b]		(63)
1-acetamido-4,6-dihydroxydibenzofuran	>10.0 (v.i.)[c]	>10.0		(63)
1-acetamido-4-methoxydibenzofuran	>10.0	>10.0		(63)
2-acetyl-7-aminodibenzofuran	2.5 (m.i.)[c]	>10.0		(63)
1-allyl-2-methoxydibenzofuran	0.625	>10.0		(63)
2-aminodibenzofuran	0.039	5.0		(61)
2-aminodibenzofuran hydrochloride	0.039	10.0[b] (tested in mouse)		(63)
4-aminodibenzofuran	0.078	10		(61)
4-aminodibenzofuran hydrochloride	0.039	10.0[b]		(63)

[a] Mg. % = mg./100 cc.

[b] Tested at 10 mg. % only.

[c] v.i. = Very insoluble, actual conc. approx. one-half to one-eighth given conc.; m.i. = moderately insoluble, actual conc. approx. one-half given conc.

Table 3 (continued)

Compound	Bacteriostatic concentration			Ref.
	Mg. %[a]	Mg. %[a] (serum)	Highest inhibiting dilution	
2-amino-3-bromodibenzofuran	10	10		(61)
1-amino-4,6-dimethoxydibenzofuran hydrochloride	>2.5 ppt. (m.i.)[c]	10.0		(63)
1-amino-4-methoxydibenzofuran hydrochloride	5.0 (v.i.)[c]	>10.0		(63)
1-bromo-4-aminodibenzofuran	0.31	10		(61)
	0.312 (v.i.)[c]	>10.0		(63)
2-bromo-3-aminodibenzofuran	10	10		(61)
	0.156 (m.i.)[c]	>10.0		(63)
2-bromo-7-aminodibenzofuran			1:400,000 (complete)	(48)
			1:1,000,000 (partial)	
2-bromodibenzofuran	>10.0 (v.i.)[c]	>10.0		(63)
4-bromodibenzofuran	1.25	>10.0		(63)
2-bromo-4-dibenzofurancarboxylic acid	10.0	10.0[b]		(63)
2-chloro-7-aminodibenzofuran			1:400,000 (complete)	(48)
			1:1,000,000 (partial)	

Table 3 (continued)

Compound	Bacteriostatic concentration			Ref.
	Mg. %[a]	Mg. %[a] (serum)	Highest inhibiting dilution	
1,4-diaminodibenzofuran hydrochloride	0.625	ppt.		(63)
2,3-diaminodibenzofuran dihydrochloride	2.5	>10.0		(63)
2,7-diaminodibenzofuran dihydrochloride	1.25 (m.i.)[c]	>10.0		(63)
2,8-diaminodibenzofuran dihydrochloride	5.0	>10.0		(63)
3,7-diaminodibenzofuran dihydrochloride	10.0	>10.0		(63)
dibenzofuran	>10.0	>10.0		(63)
2-dibenzofurancarboxylic acid, sodium salt	2.5	>10.0		(63)
4-dibenzofurancarboxylic acid	>10.0	>10.0		(63)
N-(2-dibenzofuryl)nicotinamide			<1:8,000 (serum)	(62)
			<1:8,000	
N-(2-dibenzofuryl)nicotinamidine			<1:2,000 (serum)	(62)
			<1:2,000	
1,9(?)-dibromo-2,8-dihydroxydibenzofuran	0.625	>10.0		(63)
4-diethylaminodibenzofuran hydrochloride	0.312 (m.i.)[c]	>10.0		(63)

Table 3 (continued)

Compound	Bacteriostatic concentration			Ref.
	Mg. %[a]	Mg. %[a] (serum)	Highest inhibiting dilution	
2-(β-diethylaminopropionyl)dibenzofuran hydrochloride	1.25	>10.0		(63)
1,4-dihydrodibenzofuran	5.0	>10.0		(63)
1,2-dihydro-2-dibenzofurancarboxylic acid, sodium salt	10.0	>10.0		(63)
2,8-dihydroxydibenzofuran	0.625	>10.0		(63)
3,4-dihydroxydibenzofuran	2.5	>10.0		(63)
3,7-dihydroxydibenzofuran			1:10,000 (avian)	(57)
3,7-dihydroxy-1,9-dibenzofurandicarboxylic acid			1:20,000	(58)
3,7-dihydroxy-1,9-dimethyldibenzofuran			1:40,000	(58)
			1:80,000 (avian)	(57)
3,7-dihydroxy-1,4,6,9-tetramethyldibenzofuran			1:10,000	(58)
			1:10,000 (avian)	(57)
2,8-dimethoxydibenzofuran	2.5 (m.i.)[c]	>10.0		(63)
4,6-dimethoxydibenzofuran	>10.0 (v.i.)[c]	>10.0		(63)
8-(dimethylaminomethyl)-9,10-dihydro-benzo-[b]naphtho[2,3-d]-furan-7(8H)-one hydrochloride	0.625 (v.i.)[c]	>10.0		(63)

Table 3 (continued)

Compound	Bacteriostatic concentration			Ref.
	Mg. %[a]	Mg. %[a] (serum)	Highest inhibiting dilution	
1-hydroxy-2-(3-dibenzofurylazo)-8-aminonaphthalene-3,6-disulfonic acid	1.25 (v.i.)[c]	>10.0		(63)
2-iododibenzofuran	>10.0	>10.0		(63)
4-iododibenzofuran	1.25	>10.0		(63)
3-isocaproyldibenzofuran			<1:70,000	(60)
4-(1-isoquinolyl)dibenzofuran	5.0 (v.i.)[c]	>10.0		(63)
2-methoxy-1-dibenzofurancarboxylic acid	>10.0	>10.0		(63)
2-methoxy-3-dibenzofurancarboxylic acid	10.0	>10.0		(63)
methyl-3H-benzofuro-/2,3-f/benzimidazole hydrochloride	5.0 (v.i.)[c]	10.0		(63)
methyl 2-methyl-1H-benzofuro/2,3-f/benzimidazole-8-yl-ketone hydrochloride	5.0 (v.i.)[c]	>10.0		(63)
3-nitrodibenzofuran	10.0 (v.i.)[c]	>10.0		(63)
1-n-propyl-3,7-dihydroxy-9-n-amyldibenzofuran			1:320,000 (avian)	(57)
1-n-propyl-3-methoxy-7-hydroxy-9-n-amyl-8-dibenzofurancarboxylic acid			1:40,000 (avian)	(57)

Table 3 (concluded)

Compound	Bacteriostatic concentration			Ref.
	Mg. %[a]	Mg. %[a] (serum)	Highest inhibiting dilution	
pyrido-[3,2-b]dibenzofuran hydrochloride	2.5 (v.i.)[c]	>10.0		(63)
pyrido-[3,2-a]-5-aminodibenzofuran	0.625 (v.i.)[c]	>10.0		(63)
pyrido-[2,3-c]-9-bromodibenzofuran	>10.0	>10.0		(63)
1,2,3,4-tetrahydrodibenzofuran	>10.0 (m.i.)[c]	>10.0		(63)
1,2,3,4-tetrahydro-7-dibenzofurancarboxylic acid	>10.0	>10.0		(63)
tri-(4-dibenzofuryl)-arsine	>10.0 (v.i.)[c]	>10.0		(63)
1-(p-trifluoromethylphenylazo)-2-hydroxydibenzofuran	>10.0 (v.i.)[c]	>10.0		(63)

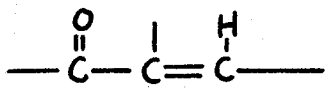
In comparing the antituberculosis potencies of compounds, it should be kept in mind that variations in medium, amount of inoculum, time and temperature of incubation and the nature of the test organism will lead to varying results. These factors are discussed thoroughly in the review previously cited.[63]

From an examination of the published data on the use of dibenzofuran derivatives as *in vitro* tuberculostatic agents, data which is presented in Table 3, it appears that perhaps

the most fruitful approaches to the discovery of significantly active dibenzofuran compounds are the preparation and testing of: dibenzofuran analogues of active diphenyl ethers and polysubstituted dibenzofurans related to didymic acid.

General antibacterial activity

It has been suggested[64] that the grouping



is one which is desirable for antibacterial activity.

Accordingly, a large number of β-aroylacrylic acids, esters and amides were synthesized[65] and tested for antibacterial action.

2,8-Dibenzofuroyldiacrylic acid was found to be inhibitory to Staphylococcus aureus at a dilution of 1:20,000. The corresponding carbazole compound inhibited the growth of the same organism at a dilution of 1:100,000. Neither of these compounds was considered particularly effective; inhibition at dilutions over 1:100,000 was taken as evidence of noteworthy activity.

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[64] W. B. Geiger and J. E. Conn, J. Am. Chem. Soc., 67, 112 (1945).

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

As part of a study[66] of mercurials derived chiefly from benzene and furan, the antiseptic potency of 4-acetoxydibenzofuran was investigated. This compound was found to inhibit the growth of S. aureus and B. coli at concentrations of the same order as those effective in the case of 5-nitro-2-furylmercuric chloride, the most promising of the compounds tested. However, the furan derivative possessed a wider margin of safety (1:50,000 to 1:1,000,000) than the dibenzofuran compound.

The synthesis and testing of 2,8-diamidinodibenzofuran (2,8-diguanyldibenzofuran) was undertaken[67] because of the structural resemblance of this compound to di-(p-amidinodiphenyl)ether. This latter compound previously had been shown to be active against Trypanosoma rhodesiense infections in mice. 2,8-Diamidinodibenzofuran cured infections of T. congolense and T. brucei in mice when administered subcutaneously in doses approaching the maximum tolerated.

Eleven dibenzofuran-substituted guanidines have been reported in a patent[68] to be bactericidal, but no further details are available. These compounds are listed in Table 4.

Shibata and co-workers[57] investigated the action of didymic acid and related compounds on S. aureus as well as on

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[66] C. Handley, N. M. Phatak and C. D. Leake, Univ. Calif., Pub. Pharmacol., 1, 175 (1936) [C. A., 33, 8802 (1939)].

[67] J. S. Moffatt, J. Chem. Soc., 625 (1951).

[68] U. S. Patent 2,191,860 [C. A., 34, 4528 (1940)].

Table 4

General Antibacterial Activity of Dibenzofuran and Derivatives

Compound	Organism	Highest inhibiting dilution	Ref.
4-acetoxydibenzofuran	S. aureus	1:30,000	(66)
	B. coli	ca. 1:59,000	
x-bromo-3-(β-diethyl-aminoethylamino)-dibenzofuran	amoebicidal		(34,35)
2-bromo-3-guanylguanido-dibenzofuran	bactericidal		(68)
2,8-diamidinodibenzo-furan	T. congolense		(67)
	T. brucei		
dibenzofuran	S. aureus	1:5,000	(57)
2,8-dibenzofuroyldi-acrylic acid	S. aureus	1:20,000	(65)
3-[β-(β'-diethyl-aminoethoxy)ethyl-amino]dibenzofuran	amoebicidal		(34,35)
3-bis-[β-(β'-diethyl-aminoethoxy)ethyl]-aminodibenzofuran	amoebicidal		(34,35)
3-(β-diethylaminoethyl-amino)dibenzofuran	amoebicidal		(34,35)
3-bis-(β-diethylamino-ethyl)aminodibenzo-furan	amoebicidal		(34,35)
2,4-bis-(β-diethyl-aminoethylamino)-dibenzofuran	amoebicidal		(34,35)

Table 4 (continued)

Compound	Organism	Highest inhibiting dilution	Ref.
3,7-bis-(β-diethylaminoethylamino)-dibenzofuran	amoebicidal		(34,35)
3-[(diethylaminoethyl)-guanylguanido]-dibenzofuran	bactericidal		(68)
3,7-bis-[(diethylaminoethyl)guanylguanido]-dibenzofuran	bactericidal		(68)
3-[β-(β'-diethylaminoethylthiol)ethylamino]-dibenzofuran	amoebicidal		(34,35)
3,7-dihydroxydibenzofuran	S. aureus	1:5,000	(57)
2,8-dimethyl-3,7-bis-(guanylguanido)-dibenzofuran	bactericidal		(68)
1,9-dimethyl-3,7-dihydroxydibenzofuran	S. aureus	1:80,000	(57)
1,9-dimethyl-3,7-dimethoxydibenzofuran	S. aureus	<1:5,000	(57)
2-(guanylguanido)-dibenzofuran	bactericidal		(68)
3-(guanylguanido)-dibenzofuran	bactericidal		(68)
2,7-bis-(guanylguanido)-dibenzofuran	bactericidal		(68)
3,7-bis-(guanylguanido)-dibenzofuran	bactericidal		(68)

Table 4 (concluded)

Compound	Organism	Highest inhibiting dilution	Ref.
2-(guanylguanido)-3-hydroxydibenzofuran	bactericidal		(68)
3-(guanylmethylguanido)-dibenzofuran	bactericidal		(68)
3-[α-hydroxy-β-(1-piperidyl)propylamino]dibenzofuran	amoebicidal		(34,35)
2-iodo-7-guanylguanidodibenzofuran	bactericidal		(68)
3-isocaproyldibenzofuran	S. aureus	<1:50,000	(60)
	E. coli	<1:50,000	
1-methyl-3,7-dihydroxydibenzofuran	S. aureus	1:40,000	(57)
3-[β-(1-piperidyl)-ethylamino]dibenzofuran	amoebicidal		(34,35)
3-bis-[β-(1-piperidyl)-ethyl]aminodibenzofuran	amoebicidal		(34,35)
1-n-propyl-3,7-diacetoxy-9-n-amyldibenzofuran	S. aureus	<1:5,000	(57)
1-n-propyl-3,7-dihydroxy-9-n-amyldibenzofuran (decarbo-nor-didymic acid)	S. aureus	1:640,000	(57)
1-n-propyl-3-methoxy-7-hydroxy-9-n-amyl-8-carboxylic acid (didymic acid)	S. aureus	1:80,000	(57)
1,4,6,9-tetramethyl-3,7-dihydroxydibenzofuran	S. aureus	<1:5,000	(57)

M. tuberculosis. Again decarbo-nor-didymic acid proved to be the most effective of the compounds tested, being inhibitory at a dilution of 1:640,000.

The 3-isocaproyldibenzofuran of Tomita and Watanabe[60] was less effective (<1:50,000) against S. aureus and E. coli than against M. tuberculosis.

The synthesis of some sulfanilamide derivatives of dibenzofuran has been reported, but their antibacterial activities are unknown.

3-(p-Aminobenzenesulfonamido)dibenzofuran and 3-(3',5'-dibromobenzenesulfonamido)dibenzofuran were synthesized by Tani and Ohsaka[69] in addition to the acetyl derivative of the former compound. Willis[17] had prepared 3-(p-aminobenzenesulfonamido)dibenzofuran and its acetyl derivative previously, but this work was not published. The 4-isomers of these two compounds were also prepared. It was reported by Willis that the great insolubility of the free amines prevented their testing.

Novelli's[70] samples of 3-(p-aminobenzenesulfonamido)dibenzofuran and the acetyl derivative were tested for physiological activity in vitro but the abstract indicates that the results were omitted from the original paper.

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[69] C. Tani and H. Ohsaka, J. Pharm. Soc. Japan, 70, 126 (1950) [C. A., 44, 5835 (1950)].

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

Carcinogenic activity

Certain heterocyclic molecules related to the active 2-aminofluorene[71] have been found to be carcinogenic. In an effort to determine whether the methylene bridge in 2-acetamidofluorene is essential for carcinogenicity, the corresponding dibenzothiophene, dibenzothiophene-5-oxide and dibenzofuran compounds were tested.[72]

3-Acetamidodibenzothiophene was found to be as carcinogenic as the fluorene compound toward the mammary gland and ear duct tissue of the rat, but introduction of the sulfoxide linkage lowered greatly the activity of the molecule. The dibenzofuran analogue had only partially diminished activity; eventually a high activity towards the mammary gland was shown as well as a somewhat reduced activity towards ear duct tissue. Unlike 2-acetamidofluorene, none of the three analogues showed activity towards the liver.

The examination of dibenzofuran itself for carcinogenic activity has not been reported, but dibenzofuran would not be expected to show this property in view of the non-carcinogenicity of fluorene.[71c]

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[71] R. H. Wilson, F. DeEds and A. J. Cox, Cancer Research, (a) 1, 595 (1941); (b) 7, 444 (1947); (c) 7, 453 (1947).

[72] E. C. Miller, J. A. Miller, R. B. Sandin and R. K. Brown, ibid., 9, 504 (1949).

The preparation of various N-trifluoroacetyl derivatives of carcinogenic amines has been reported recently.[73] Included were 3-trifluoroacetamidodibenzofuran, 3-trifluoroacetamidodibenzothiophene and 2-trifluoroacetamidofluorene. No mention was made of the carcinogenic properties of these molecules.

2-(3-Dibenzofuryl)-3-n-propylindole and 2-(3-dibenzofuryl)-3-n-butylindole have been synthesized[74] as part of a study of the chemistry of carcinogenic nitrogen compounds. These compounds were reported to be under biological investigation at the time of publication.

Phytohormonal activity

In the literature there is but one reference to the testing of dibenzofuran derivatives for use as plant hormones.

Gilman and Avakian[75] prepared 2-dibenzofurylacetic acid and 2,8-dibenzofuryldiacetic acid, the latter compound proving inactive in plant growth tests. No information was given in regard to the activity of the mono-carboxylic acid, but two related types, 2-carbazolylacetamide and 2-carbazolylacetic acid were found to be inactive.

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[73] E. Sawicki and F. E. Ray, J. Am. Chem. Soc., 75, 2266 (1953).

[74] Ng. Ph. Buu-Hoi, J. Chem. Soc., 2882 (1949).

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

The preparation of 2,8-dibenzofurandioxyacetic acid has been accomplished,[18] but this compound is too insoluble in water and ethanol to permit a satisfactory evaluation of it in phytohormonal tests.

Insecticidal and fungicidal activity

Dibenzofuran and its derivatives have been tested rather extensively by entomologists, and the accumulated data indicate that members of this series are quite satisfactory insecticides and fungicides.

No attempt will be made here to discuss the many applications of dibenzofuran compounds in this field. This information is presented in Table 5.

Table 5 was compiled to a large extent from material collected in Frear's[76] excellent summary. A recent publication[77] by this same author which was unavailable to the writer at the time of preparation of this dissertation may contain further examples of the use of dibenzofuran compounds as insecticides.

Since the use of dibenzofuran as an insecticide in spray form might result in a public health hazard in the form of

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[76]D. E. H. Frear, "A Catalogue of Insecticides and Fungicides", Chronica Botanica Co., Waltham, Mass., Vol. I, 1947, Vol. II, 1948.

[77]D. E. H. Frear, "Pesticide Handbook", College Science Publishers, State College, Pa., 1954.

spray residue, the effect of this compound on albino rats was studied.[78]

The highest concentration of dibenzofuran (8,000 ppm.) in the basic ration of the rats produced no retardation of growth. Food intake was not appreciably altered, and no animals exhibited abnormalities of behavior or activity. An increase in water intake and urine output was observed but not until 15 days after commencement of the experiment. Abdominal fat increased, but there were no significant abnormalities in the livers, spleens, hearts and adrenals of the rats; the kidneys showed fine brown pigment granules.

It was concluded that the use of dibenzofuran would be unlikely to cause a spray residue problem, unless the compound were changed to a more toxic one by weathering or other conditions.

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[78] J. O. Thomas, R. H. Wilson and C. W. Eddy, Food Research, 5, 23 (1940).

Table 5

Dibenzofuran and Some Derivatives as Insecticides and Fungicides

Compound	Organism	Toxicity	Ref.
2-acetyldibenzofuran	mosquito larvae	58% at 20 ppm. after 16 hr.	(79)
3-aminodibenzofuran	mosquito larvae	48% at 5 ppm. after 16 hr.	(79)
	mosquito larvae	50% or more at 5 ppm. within 16 hr.	(80)
	imported cabbage worm	low mortality after 24 hr.	(81)
	eggs of furniture carpet beetle	ineffective	(82)
3-chlorodibenzofuran	mosquito larvae	50% at 5 ppm. after 16 hr.	(79)
	mosquito larvae	50% or more at 5 ppm. within 16 hr.	(80)
	imported cabbage worm	low mortality after 24 hr.	(81)

[79] D. E. Fink, L. E. Smith, D. L. Vivian and H. V. Claborn, U. S. D. A. Bur. Entomol. and Plant Quar., Div. Insecticide Invest., Mimeo Pub. E-425 (1938).

[80] D. E. Fink and D. L. Vivian, J. Econ. Entomol., 29, 804 (1936).

[81] F. L. Campbell, W. N. Sullivan, L. E. Smith and H. L. Haller, ibid., 27, 1176 (1934).

[82] W. Colman, U. S. D. A. Bur. Entomol. and Plant Quar., Div. Insecticide Invest., Mimeo Pub. E-592 (1943).

Table 5 (continued)

Compound	Organism	Toxicity	Ref.
2-chloro-7-nitrodibenzofuran	mosquito larvae	0% at 100 ppm.	(79)
dibenzofuran	mosquito larvae	80% at 5 ppm. after 16 hr.	(79)
	mosquito larvae	50% or more at 5 ppm. within 16 hr.	(80)
	mosquito larvae	nearly 100% at 5 ppm. in 5 hr.	(81)
	German roach	some toxicity	(83)
	powder-post beetle	toxic	(84)
	Hylotrupes bajulus	toxic	(84)
	Trombicula mites (chiggers)	100% at 100 lb./acre	(85)
	fungicide and insecticide		(86)

[83] G. E. Gould, Pests, 11, 12 (1943).

[84] B. Schulze and G. Becker, Holzforschung, 2, 97 (1948) [C. A., 43, 4417 (1949)].

[85] J. P. Linduska, F. A. Morton and W. C. McDuffie, J. Econ. Entomol., 41, 43 (1948).

[86] German Patent 355,206 [Chem. Zentr., 93, IV, 429 (1922)].

Table 5 (concluded)

Compound	Organism	Toxicity	Ref.
dibenzofuran	screwworm	0.05-0.08% minimum lethal concentration	(87)
	screwworm	high	(88)
3-nitrodibenzofuran	screwworm	non-toxic	(89)
	imported cabbage worm	low mortality after 24 hr.	(81)
	mosquito larvae	0% at 100 ppm.	(79)
1,2,3,4-tetrahydro-7-acetyldibenzofuran	mosquito larvae	96% at 20 ppm. after 16 hr.	(79)
1,2,3,4-tetrahydro-7-aminodibenzofuran	mosquito larvae	60% at 40 ppm. after 16 hr.	(79)
1,2,3,4-tetrahydro-7-nitrodibenzofuran	mosquito larvae	20% at 100 ppm. after 16 hr.	(79)

[87] L. E. Smith and R. Melvin, J. Econ. Entomol., 36, 475 (1943).

[88] H. E. Parish and E. F. Knipling, ibid., 35, 70 (1942).

[89] R. C. Bushland, ibid., 33, 669 (1940).

Miscellaneous observations

A study[90] of the choleretic potencies of a variety of carboxylic acids, most of them aliphatic acids ω-substituted by polycyclic or heterocyclic systems, indicated β-(1-methoxy-4-naphthoyl)propionic acid to be most potent. This compound had a M.P. (molecular potency) of 115 and a G.P. (gravimetric potency) of 180. Dehydrocholic acid was arbitrarily given a value of 100.

β-(2-Dibenzofuroyl)propionic acid (M.P. 30, G.P. 44), β-(2-dibenzofuroyl)acrylic acid (M.P. 14, G.P. 21) and β-bromo-β-(2-dibenzofuroyl)propionic acid (M.P. 5, G.P. 6) were not found to possess appreciable choleretic strength.

The salt formed from ephedrine hydrochloride and 2-dibenzofuransulfonic acid has been prepared[91] but no physiological data have been published.

Barker, et.al.[92] studied the thyroxine-inhibiting effect of a variety of compounds including 3-dimethylaminomethyldibenzofuran hydrochloride. They found the appreciable potency of this compound difficult to explain on a structural basis. The compound could not be administered subcutaneously at high

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[90] M. J. Gunter, K. S. Kim, D. F. Magee, H. Ralston and A. C. Ivy, J. Pharmacol. Exptl. Therap., 99, 465 (1950).

[91] C. E. Miller, J. Am. Chem. Soc., 72, 2303 (1950).

[92] S. B. Barker, C. E. Kiely, Jr., H. B. Dirks, Jr., H. M. Klitgaard, S. C. Wang and S. Wawzonek, J. Pharmacol. Exptl. Therap., 99, 202 (1950).

dosage because of its toxicity and oral ingestion was without effect. Thus experimentation with this compound was limited.

Some dibenzofuran compounds have been subjected to tests designed to reveal organic structures which are particularly toxic to rats.[93] The minimum lethal doses (mg./kg.) of the dibenzofuran compounds were too great to recommend these compounds as rodenticides. The values found were x,x-dichlorodibenzofuran, 250; 3-nitrodibenzofuran, >500; and 2-(dicyanophosphino)dibenzofuran, >500.

Three dibenzofuran compounds were also tested for their repellency indices.[94] 3-Aminodibenzofuran was rated at 79, 3-nitrodibenzofuran at -5 and x-(3-dibenzofuryl)stearic acid at -101. Only compounds having a repellancy index of 85 or higher were reserved for further study.

There is in the literature one report concerning the metabolism of dibenzofuran. Christomanos[95] injected dibenzofuran in olive oil subcutaneously into rabbits. He found that a considerable amount of hippuric acid was excreted. As compared to the control period, the amount of benzoic acid

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[93] J. B. DeWitt, E. Bellack, C. W. Klingensmith, J. C. Ward and R. Treichler, Chemical-Biological Coordination Center, Review No. 5, National Research Council, Washington, D. C., 1953, pp. 1-47.

[94] E. Bellack, J. B. DeWitt and R. Treichler, Chemical-Biological Coordination Center, Review No. 5, National Research Council, Washington, D. C., 1953, pp. 48-156.

[95] A. A. Christomanos, Z. physiol. Chem., 181, 182 (1929) /C. A., 23, 3494 (1929)/.

excreted was slightly greater but no salicylic acid or o-hydroxyhippuric acid was found. The mechanism of metabolism suggested involves the cleavage of dibenzofuran at the ether linkage with destruction of the nucleus which retains the oxygen atom. The benzoic acid formed is detoxified in the usual manner with glycine.

Derivatives of Dibenzofuran

Table 6 is an addition to the compilations of known derivatives of dibenzofuran which have appeared in previous dissertations[13,14,17,20,23] from this laboratory. In the Table are entered all dibenzofuran derivatives which were listed in the 1952 Index to Chemical Abstracts as well as most, if not all, of those dibenzofuran compounds listed in the Chemical Abstracts of 1953 and 1954 through the issue of Vol. 48, No. 10.

The compounds of Table 6 have been named according to the style indicated in the Introduction to this dissertation. In assembling this information, it was assumed that the melting points were uncorrected unless the original literature indicated otherwise.

Table 6

Derivatives of Dibenzofuran

Compound	M.P. (°C.)	Ref.
Monosubstituted dibenzofurans		
2-ω-acetamidoacetyldibenzofuran	192-193	(96)
2-acetyldibenzofuran	82-83	(96)
p-aminoacetanilide salt of 2-dibenzofuransulfonic acid	290	(97)
2-ω-aminoacetyldibenzofuran hydrochloride	265-267 dec.	(96)
3-aminodibenzofuran	99-100	(23)
4-aminodibenzofuran	83-84	(23,49)
3-aminodibenzofuran salt of p-toluenesulfonic acid	255-256 dec.	(98)
o-aminodicyclohexyl salt of 2-dibenzofuransulfonic acid	213-255	(97)
aniline salt of 2-dibenzofuran-sulfonic acid	258-260	(97)
3,3'-azoxydibenzofuran	271	(98)
2-benzamidodibenzofuran	185-186	(96)

[96]This dissertation.

[97]R. Wendland, J. Rode and R. Meintzer, J. Am. Chem. Soc., 75, 3606 (1953).

[98]L. Bauer, J. N. Baxter, J. Cymerman and W. J. Sheldon, J. Chem. Soc., 1184 (1952).

Table 6 (continued)

Compound	M.P. (°C.)	Ref.
2-benzoyldibenzofuran	136-138	(96)
2-benzoyldibenzofuran oxime	158.5-159.5	(96)
2-ω-bromoacetyldibenzofuran	105.5-106.5	(96)
2-bromodibenzofuran	107-108.5	(96)
	108-109	(23)
2-(α-bromoethyl)dibenzofuran	83-84	(39)
n-butylamine salt of 2-dibenzofuran-sulfonic acid	207-208	(97)
2-chloroacetyldibenzofuran	b.p. 205-209.5 at 1.2-2.0 mm.	(96)
o-chloroaniline salt of 2-dibenzofuransulfonic acid	228-230	(97)
2-cyanodibenzofuran	140-141	(96)
3-cyanodibenzofuran	109-116	(23)
cyclohexylamine salt of 2-dibenzofuransulfonic acid	214-216	(97)
di-benzidine salt of 2-dibenzofuran-sulfonic acid	>300	(97)
2-dibenzofurancarboxylic acid	255.5-257.7	(96)
3-dibenzofurancarboxylic acid	270-272	(23)
2-dibenzofurancarboxylic acid amide	220-221	(96)
2-dibenzofurancarboxylic acid anilide	164-165.5	(96)
4-dibenzofurancarboxylic acid anilide	142.4-144.5	(96)

Table 6 (continued)

Compound	M.P. (°C.)	Ref.
2-dibenzofurancarboxylic acid benzenesulfonhydrazide	220-221.5	(96)
4-dibenzofurancarboxylic acid benzenesulfonhydrazide	242-243	(96)
2-dibenzofurancarboxylic acid hydrazide	210-212	(96)
4-dibenzofurancarboxylic acid hydrazide	174-175	(96)
2-dibenzofuransulfonic acid	---	(97)
N-(2-dibenzofuryl)nicotinamide	220	(62)
N-(2-dibenzofuryl)nicotinamide salt of p-toluenesulfonic acid	213	(62)
N-(2-dibenzofuryl)nicotinamidine	217.5	(62)
2-dibenzofuryltriphenylsilane	137.5-138.5	(99)
4-dibenzofuryltriphenylsilane	153-154	(99)
di-n-butylamine salt of 2-dibenzofuransulfonic acid	164	(97)
2-ω-dichloroacetamidodibenzofuran	167-169	(96)
dicyclohexylamine salt of 2-dibenzofuransulfonic acid	239-240	(97)
di-2,4-diaminophenol salt of 2-dibenzofuransulfonic acid	250 dec.	(97)
di-ethylenediamine salt of 2-dibenzofuransulfonic acid	>305	(97)
di-hydrazine salt of 2-dibenzofuransulfonic acid	260 dec.	(97)

[99]Dr. R. H. Meen, unpublished studies.

Table 6 (continued)

Compound	M.P. (°C.)	Ref.
di-isobutylamine salt of 2-dibenzofuransulfonic acid	168	(97)
N,N-dimethylaniline salt of 2-dibenzofuransulfonic acid	61-62	(97)
di-m-phenylenediamine salt of 2-dibenzofuransulfonic acid	280-290 dec.	(97)
di-p-phenylenediamine salt of 2-dibenzofuransulfonic acid	>305	(97)
diphenylguanidine salt of 2-dibenzofuransulfonic acid	195-196	(97)
N-ethylaniline salt of 2-dibenzofuransulfonic acid	128-129	(97)
ethyl 2-dibenzofuranoxyacetate	54-54.5	(96)
guanidine salt of 2-dibenzofuransulfonic acid	>310	(97)
2-[α-(β'-hydroxyethylamino)ethyl]-dibenzofuran hydrochloride	168-170	(39)
8-hydroxyquinoline salt of 2-dibenzofuransulfonic acid	207-208	(97)
2-iododibenzofuran	110-111	(96)
3-isocaproyldibenzofuran	---	(60)
N-methylaniline salt of 2-dibenzofuransulfonic acid	148-149	(97)
methyl 2-dibenzofurancarboxylate	80.5-82.5	(96)
α-naphthylamine salt of 2-dibenzofuransulfonic acid	260 dec.	(97)
β-naphthylamine salt of 2-dibenzofuransulfonic acid	245-246 dec.	(97)

Table 6 (continued)

Compound	M.P. (°C.)	Ref.
m-nitroaniline salt of 2-dibenzofuransulfonic acid	250 dec.	(97)
p-nitroaniline salt of 2-dibenzofuransulfonic acid	240 dec.	(97)
2-nitrodibenzofuran	151-152	(23,49)
3-nitrodibenzofuran	181-182	(23,49)
	181.5	(96)
	181	(97)
4-nitrodibenzofuran	138-139	(23,49)
o-phenylenediamine salt of 2-dibenzofuransulfonic acid	225 dec.	(97)
phenylhydrazine salt of 2-dibenzofuransulfonic acid	193-194 dec.	(97)
2-[α-(1-piperidyl)ethyl]dibenzofuran hydrochloride	160-163	(39)
quinoline salt of 2-dibenzofuransulfonic acid	195-196	(97)
semicarbazide salt of 2-dibenzofuransulfonic acid	205-215	(97)
sulfanilamide salt of 2-dibenzofuransulfonic acid	245-246 dec.	(97)
tetra-hexamethylenetetramine salt of 2-dibenzofuransulfonic acid	158-159	(97)
o-toluidine salt of 2-dibenzofuransulfonic acid	242-243 dec.	(97)
m-toluidine salt of 2-dibenzofuransulfonic acid	205-206	(97)
p-toluidine salt of 2-dibenzofuransulfonic acid	232-234	(97)

Table 6 (continued)

Compound	M.P. (°C.)	Ref.
tri-n-butylamine salt of 2-dibenzofuransulfonic acid	117-118	(97)
3-trifluoroacetamidodibenzofuran	204-205	(73)
urea salt of 2-dibenzofuransulfonic acid	203 dec.	(97)
Disubstituted dibenzofurans		
3-acetyl-4-methoxydibenzofuran	69.5-70.5	(96)
dl-alanine salt of 2-dibenzofuransulfonic acid	250-300 dec.	(97)
α-aminoisobutyric acid salt of 2-dibenzofuransulfonic acid	250-300 dec.	(97)
aniline salt of 2-dibenzofuransulfonic acid	258-260 dec.	(97)
2-bromo-7-acetamidodibenzofuran	220-220.5	(23,49)
2-bromo-7-aminodibenzofuran	131.5-133	(23,49)
p-bromoaniline salt of 3-nitro-8-dibenzofuransulfonic acid	258-266 dec.	(97)
2-bromo-8-dibenzofurancarboxylic acid	334.5-336.5	(96)
2-bromo-6-dibenzofurancarboxylic acid benzenesulfonhydrazide	228-229	(96)
2-bromo-6-dibenzofurancarboxylic acid hydrazide	198-200	(96)
2-bromo-7-nitrodibenzofuran	250-251	(23,49)
	251.5-253	(96)
2-bromo-8-nitrodibenzofuran	210-212	(23,49)

Table 6 (continued)

Compound	M.P. (°C.)	Ref.
n-butylamine salt of 3-nitro-8-dibenzofuransulfonic acid	264	(97)
creatinine salt of 3-nitro-8-dibenzofuransulfonic acid	258	(97)
l-cysteine salt of 3-nitro-8-dibenzofuransulfonic acid	219	(97)
di-l-arginine salt of 3-nitro-8-dibenzofuransulfonic acid	235-236	(97)
2,8-dibenzamidodibenzofuran	293-296	(96)
2,8-dibenzofurandicarboxylic acid	440-442	(96)
4,6-dibenzofurandicarboxylic acid	---	(100)
2,8-dibenzoyldibenzofuran	167-168.5	(96)
2,8-dibenzoyldibenzofuran dioxime	231.5-232 dec.	(96)
2,8-dibromodibenzofuran	192-193	(23,49)
	194-195	(96)
di-n-butylamine salt of 3-nitro-8-dibenzofuransulfonic acid	167	(97)
2,8-dicyanodibenzofuran	304-305	(96)
di-l-cystine salt of 3-nitro-8-dibenzofuransulfonic acid	215	(97)
di-l-histidine salt of 3-nitro-8-dibenzofuransulfonic acid	248	(97)
4,6-dimethyldibenzofuran	87 b.p. 313 at 757 mm.	(100)

[100] O. Kruber and A. Raeithel, Chem. Ber., 85, 327 (1952).

Table 6 (continued)

Compound	M.P. (°C.)	Ref.
x,x'-dimethyldibenzofuran	45-46	(100)
y,y'-dimethyldibenzofuran	58-59	(100)
dimethyl 4,6-dibenzofurandicarboxylate	162-162.5	(100)
2-hydroxy-3-dibenzofurancarboxylic acid 2,5-dimethoxyanilide	---	(101)
dl-isoleucine salt of 3-nitro-8-dibenzofuransulfonic acid	246	(97)
l-leucine salt of 3-nitro-8-dibenzofuransulfonic acid	260-262 dec.	(97)
dl-lysine salt of 3-nitro-8-dibenzofuransulfonic acid	250-300 dec.	(97)
dl-methionine salt of 3-nitro-8-dibenzofuransulfonic acid	250-300 dec.	(97)
4-methoxy-1-dibenzofurancarboxaldehyde	104-105	(102)
β-(4-methoxy-1-dibenzofuran)acrylic acid	281-282	(102)
γ-(4-methoxy-1-dibenzofuran)butyric acid	165	(102)
4-methoxy-1-dibenzofurancarboxylic acid	280-281	(102)
β-(4-methoxy-1-dibenzofuran)-propionic acid	176-178	(102)

[101] British Patent 662,573 [C.A., 46, 6394 (1952)].

[102] H. Gilman, S. Avakian, J. A. Hogg and R. G. Johnson, J. Am. Chem. Soc., 75, 6310 (1953).

Table 6 (continued)

Compound	M.P. (°C.)	Ref.
β-(4-methoxy-1-dibenzofuroyl)-propionic acid	224-225	(102)
4-methyl-6-dibenzofurancarboxylic acid	233-235	(100)
3-nitro-8-dibenzofurancarboxylic acid	310-325	(96)
3-nitro-8-dibenzofuransulfonic acid	chars 240	(97)
3-nitro-4-hydroxydibenzofuran	194-194.5	(102)
dl-norleucine salt of 3-nitro-8-dibenzofuransulfonic acid	250-300 dec.	(97)
dl-phenylalanine salt of 3-nitro-8-dibenzofuransulfonic acid	247	(97)
p-toluidine salt of 3-nitro-8-dibenzofuransulfonic acid	250 dec.	(97)
dl-tryptophan salt of 3-nitro-8-dibenzofuransulfonic acid	250-300 dec.	(97)
urea salt of 3-nitro-8-dibenzofuran-sulfonic acid	>300 dec.	(97)
dl-valine salt of 3-nitro-8-dibenzo-furansulfonic acid	250-300 dec.	(97)
<u>Trisubstituted dibenzofurans</u>		
β-(2-bromo-4-methoxy-1-dibenzo-furoyl)propionic acid	194-195	(102)
2,x-dibromo-3-acetamidodibenzofuran	233-236	(23)
2,8-dibromo-3-acetamidodibenzofuran	235-236	(23,49)
2,8-dibromo-3-aminodibenzofuran	182-183	(23,49)
2,8-dibromo-x-nitrodibenzofuran	332-335	(23)

Table 6 (concluded)

Compound	M.P. (°C.)	Ref.
γ-(4,6-dimethoxy-1-dibenzofuran)-butyric acid	197-198	(102)
4,6-dimethoxy-1-dibenzofurancarboxylic acid	297-298	(102)
β-(4,6-dimethoxy-1-dibenzofuroyl)-propionic acid	241-242	(102)
γ-(3-nitro-4-methoxy-1-dibenzofuran)-butyric acid	169-170	(102)
3-nitro-4-methoxy-1-dibenzofurancarboxylic acid	269-270	(102)
Tetrasubstituted dibenzofurans		
3,7-dihydroxy-1,9-dibenzofurandicarboxylic acid	---	(58)
3,7-dihydroxy-1,9-dimethyldibenzofuran	---	(58)
2,4,6,8-tetranitrodibenzofuran	252	(103)
Hexasubstituted dibenzofurans		
3,7-dihydroxy-1,4,6,9-tetramethyldibenzofuran	---	(58)

[103] H. Zahn and H. Zuber, Chem. Ber., 86, 172 (1953).

EXPERIMENTAL[104,105]

Derivatives of Dibenzofuran

Monobromination of dibenzofuran

Method 1. To a well-stirred solution of 168 g. (1.00 mole) of dibenzofuran in 600 ml. of carbon tetrachloride were added 160 g. (1.00 mole) of bromine. The addition which was carried out over a period of three hours was performed at room temperature. The reaction mixture was allowed to stand for 10.5 hours without stirring, then it was stirred and refluxed for one hour. The carbon tetrachloride and excess bromine were removed by distillation, and the remaining material (231 g.) was vacuum distilled. Two fractions were collected: 25.5 g., b.p. range 100-162° at 0.2 mm., m.p. range 54-64° and 188.5 g., b.p. range 162-182° at 0.2 mm., m.p. range 78-98°. It was necessary to recrystallize the second fraction four times from petroleum ether (b.p. range 60-70°) to obtain a product of m.p.

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[104] All melting points herein reported are uncorrected values; unless otherwise stated, the melting points were determined by the capillary tube method at the heating rate of 1°/minute in the vicinity of the melting point.

[105] The infrared spectra of the compounds described were obtained by use of the Baird Double Beam Infrared Spectrophotometer of the Institute for Atomic Research, Iowa State College. The writer wishes to thank Dr. Marvin Margoshes, and Messrs. Richard M. Hedges and Robert D. Kross for the determination of and assistance in the interpretation of the spectra.
All spectra were determined on Nujol mulls of the compounds, unless it is otherwise indicated.

107-108.5°. The 73.3 g. of pure material represented a yield of 29.7%.

The mother liquors from the recrystallizations were worked up in an attempt to increase the yield. This effort produced an additional 58.1 g. of less pure 2-bromodibenzofuran, m.p. range 98-103°.

The above procedure is essentially that of Bywater[6] who reported a 62% yield of product melting over the range 98-102°.

Method 2. This procedure is that of Buu-Hoi and Royer[106] who reported an "excellent yield" of 2-bromodibenzofuran by the bromination of the heterocycle in glacial acetic acid.

A solution of 10.0 g. (0.059 mole) of dibenzofuran in 150 ml. of glacial acetic acid was cooled to 0° by means of an ice bath, and a solution of 9.4 g. (0.059 mole) of bromine in 50 ml. of glacial acetic acid was added over a period of one hour with stirring. An iodine crystal was added to facilitate bromination. When the addition had been completed, the reaction mixture was poured into ice water. The yellow precipitate was washed free of acid and excess bromine with water and sodium bisulfite solution. The weight of crude 2-bromodibenzofuran was 12.1 g. Vacuum distillation gave two fractions: 7.0 g., b.p. range 98-130° at 0.1 mm. and 4.3 g. (29.5%), b.p. range 130-135° at 0.1 mm. The second fraction melted from 98°

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[106]Ng. Ph. Buu-Hoi and R. Royer, Rec. trav. chim., 67, 175 (1948).

to 104°. Recrystallization from petroleum ether (b.p. range 60-70°) raised the melting point to 106.5-109°.

The infrared spectrum of the 2-bromo compound showed the 1,2,4-substitution band at 12.32μ.

Dibenzofuran itself has been examined by infrared and the following assignments made: 8.34μ, ether linkage; 13.27μ, ortho disubstitution and 13.85μ, presently unassigned.

Preparation of 2-iododibenzofuran

The iodination of dibenzofuran was accomplished by the procedure previously published.[107]

A mixture of 50.4 g. (0.300 mole) of dibenzofuran and 38.1 g. (0.300 mole) of iodine in 21 ml. of conc. nitric acid and 250 ml. of chloroform was refluxed and stirred for 4.6 hours. The chloroform layer was separated and washed with sodium bisulfite solution, then with water. The chloroform solution was dried over anhydrous sodium sulfate for 48 hours, then the solvent was removed by distillation. The crude 2-iododibenzofuran melted over the range 63° to 93° and weighed 76.0 g. On distillation *in vacuo*, two fractions were obtained: 11.34 g., b.p. range 124-153° at 0.35 mm., m.p. range 60-66° and 57.30 g., b.p. range 153-175° at 0.35 mm., m.p. range 76-96°. Recrystallization of the second fraction from ethanol-petroleum ether

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

(b.p. range 60-70°) yielded 30.0 g. (34.0%) of white plates, m.p. 107-110°. Concentration of the mother liquors gave 7.5 g. of less pure compound, m.p. range 102-108°. The material melting from 107° to 110° was recrystallized from the same solvent to give pure 2-iododibenzofuran, m.p. 111-112°.

The infrared spectrum of this compound possessed an absorption band at 12.42μ characteristic of 1,2,4-substitution.

Preparation of 2-chlorodibenzofuran (attempted)

An attempt was made to adapt the procedure[106] for the preparation of 2-bromodibenzofuran by the action of N-bromosuccinimide on dibenzofuran to the synthesis of 2-chlorodibenzofuran. The N-chlorosuccinimide was generously supplied by the National Aniline Division of Allied Chemical and Dye Corporation.

A mixture of 25.2 g. (0.15 mole) of dibenzofuran and 40.0 g. (0.30 mole) of N-chlorosuccinimide in 200 ml. of carbon tetrachloride was heated at reflux for 42 hours. At the conclusion of the heating period the reaction mixture was yellow in color. The solid which had settled out was filtered off and the yellow carbon tetrachloride solution was washed twice with 10% sodium hydroxide solution, then with water. The organic layer was dried over anhydrous calcium chloride.

The 38.0 g. of solid material which had been filtered from the reaction mixture was thought to be a mixture of 2-chlorodibenzofuran, 2,8-dichlorodibenzofuran and succinimide.

Accordingly, it was extracted with dilute sodium hydroxide, and the insoluble material was added to the carbon tetrachloride solution being dried.

The carbon tetrachloride was removed by distillation, finally at 14 mm., and the residue was distilled *in vacuo*. The sole fraction collected boiled from 80° to 94° at 0.15-0.20 mm. It weighed 22.1 g. and melted over the range 65-77°. On recrystallization of this crude material from petroleum ether (b.p. 60-70°), 7.39 g. of white plates were obtained, m.p. range 77-81.5°. A mixed melting point determination indicated this material to be dibenzofuran.

Preparation of 2-cyanodibenzofuran

This nitrile was prepared for the first time by Oatfield who employed the Rosenmund-von Braun synthesis.[108,109] Oatfield[4] obtained a 70% yield (m.p. 137°) in the more successful of two trials. Bywater[6] in a four-fold larger run secured a 39.5% yield of less pure nitrile, m.p. 128-131°. A melting point of 136° was reported by Kirkpatrick.[110]

The fusion method employed by these workers was used in initial preparations of the nitrile. It was found to be more advantageous, however, to employ quinoline as a solvent.

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[108] K. W. Rosenmund and E. Struck, Ber., 52, 1749 (1919).

[109] J. v. Braun and G. Manz, Ann., 488, 111 (1931).

[110] Dr. W. H. Kirkpatrick, private communication.

Fusion method. A mixture of 49.4 (0.200 mole) of 2-bromodibenzofuran and 43.0 g. (0.240 mole as dimer) of cuprous cyanide was heated and stirred for six hours at 270°. The hot molten mass was poured into a casserole to cool. The crude material (71.7 g.) was pulverized and extracted with benzene in a Soxhlet extractor for 22.5 hours. On evaporation of the solvent there remained 19.1 g. (49.2%) of light golden brown needles, m.p. range 124-130°. Two recrystallizations from ethanol gave 9.2 g. (23.8%) of orange needles, m.p. 137.5-138.5°. From the mother liquors were obtained an additional 3.7 g. of nitrile, m.p. 136-138.5°, softening at 134°.

Absorption bands at 4.57μ (-CN) and 12.21μ (1,2,4-substitution) were present in the infrared spectrum of the nitrile.

Triethylene glycol as reaction medium. The use of triethylene glycol was suggested by the report[111] that this glycol apparently actively participates in the reductive debromination of dibenzofuran and by the use[112] of ethylene glycol as a solvent in the synthesis of aliphatic nitriles.

A mixture of 12.4 g. (0.050 mole) of 2-bromodibenzofuran and 4.9 g. (0.100 mole) of sodium cyanide was suspended in 200 ml. of triethylene glycol, and the reaction mixture was heated

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[111] H. Gilman, D. L. Esmay and R. K. Ingham, J. Am. Chem. Soc., 73, 470 (1951).

[112] R. N. Lewis and P. V. Susi, ibid., 74, 840 (1952).

and stirred for four hours at 210-220°. The reaction mixture which now was orange-brown in color was poured into a large volume of water. The insoluble material was filtered, washed with copious amounts of water and dried to give 12.7 g. of a tan powder, m.p. range 100-107° with residue. Recrystallization from petroleum ether (b.p. range 60-70°) gave 5.6 g. of 2-bromodibenzofuran, m.p. 108-109.5°.

Quinoline as solvent.

Method 1. A slurry of 24.7 g. (0.100 mole) of 2-bromodibenzofuran and 21.5 g. (0.120 mole as dimer) of cuprous chloride in 80 ml. of redistilled quinoline was placed in a three-neck flask equipped with air condenser, stirrer and thermometer. In an atmosphere of nitrogen and with vigorous stirring, the reactants were heated at 180° for 24 hours and at 150° for three additional hours. The reaction mixture solidified at about 160° as the temperature was being brought to 180°; however, it reliquified in a short time. At the conclusion of the heating period, the mixture was allowed to cool somewhat; then it was poured into a large volume of conc. ammonium hydroxide. Benzene (200 ml.) was added in several portions to dissolve the organic material, and the benzene layers washed with water until the blue color of the copper complex had been removed. After separation of the aqueous and benzene phases, the latter were dried over anhydrous magnesium sulfate. Filtration of the extract was followed by the removal

of the benzene by distillation at atmospheric pressure and finally at aspirator vacuum. The quinoline was distilled off at 0.2 mm. The black residue which remained was recrystallized from ethanol, Norit A being used for decolorization. Brown colored needles, 6.80 g., m.p. 137-139°, were obtained. A second recrystallization from ethanol raised the m.p. to 139-140.5° (4.30 g.). From the mother liquors of the recrystallizations were obtained 3.20 g. of nitrile, m.p. 139.5-141°. Total yield: 7.50 g., 38.8%.

Method 2. The slurry of 24.7 g. (0.100 mole) of 2-bromodibenzofuran and 21.5 g. (0.120 mole as the dimer) in 100 ml. of quinoline was heated at 180° for 24 hours under nitrogen. The black solution was poured into a 600 ml. beaker, and after cooling, the solid was boiled up with 200 ml. of 1:1 hydrochloric acid. The material which did not dissolve was filtered off and dried. The brown powder weighed 21.9 g. (113%) and melted at 136-137.5°, softening at 134°. Recrystallization from ethanol with the use of Norit A gave 10.40 g. (53.8%) of needles, m.p. 140-141°. Concentration of the mother liquors gave several additional crops of needles totaling 4.89 g., m.p. 138-140°. The total yield of pure nitrile was 15.29 g. (79.1%).

Method 3. The reaction was carried out in the same manner as previously (method 2) except for the use of 29.4 g.

(0.100 mole) of 2-iododibenzofuran as the halide. Also, the reaction mixture was heated at 180° for 48 hours. The brown powder which resulted from the acid treatment was extracted three times with 150 ml. of benzene in a Soxhlet extractor. Each extraction period was 12 hours. The material remaining in the thimble was removed, thoroughly ground in a mortar and extracted with benzene for an additional 24 hours. The extracts were violet in color, due possibly to the presence of free iodine formed by air oxidation of the iodide ion at the high reaction temperature. Evaporation of the benzene from the combined extracts left 15.9 g. of brown needles, m.p. range 120-128°. Recrystallization of the crude material from ethanol yielded 10.46 g., m.p. range 130-137°, soft at 124°.

Variations of the methods which employed 2-bromodibenzofuran were tried, but none was as satisfactory as method 2. The choice of 190° as the reaction temperature (other conditions and the quantities of reagents remaining the same) resulted in a 42.5% yield of nitrile. When the reaction was continued for 45 minutes at 190° and for 45 minutes at 205°, the product obtained had a melting point of 115-117° (with softening at 107°) after recrystallization from ethanol. Hydrolysis in methanolic potassium hydroxide gave 8.2 g. of 2-dibenzofurancarboxylic acid, m.p. 256-259°. Had the hydrolysis and subsequent recovery of the acid been quantitative, this would have corresponded to a yield of 38.6% of nitrile. The reaction of 0.167 mole of 2-bromodibenzofuran with 0.200 mole

of cuprous cyanide in 140 ml. of quinoline at 170° for 16 hours produced no detectable amounts of nitrile.

Hydrolysis of 2-cyanodibenzofuran

2-Cyanodibenzofuran was prepared in the usual manner from 42.4 g. (0.172 mole) of 2-bromodibenzofuran and 43.0 g. (0.240 mole as the dimer) of cuprous cyanide in 250 ml. of quinoline. The reaction was carried out at 180° for 24 hours. The crude material remaining after treatment of the reaction mixture with 400 ml. of a 1:1 hydrochloric acid solution was found to weigh 128.4 g. and it left considerable residue on ignition. A second treatment with acid gave 27.5 g. of light brown powder which left only a slight residue on ignition. This crude nitrile was not purified but hydrolyzed directly to the acid. A solution of the nitrile in 200 ml. of methanol containing 40 g. of potassium hydroxide was refluxed for 24 hours; then the reaction mixture was poured into twice its volume of water, Norit A was added, and the solution was filtered at its boiling point. The filtrate was acidified with hydrochloric acid, whereupon a white gelatinous precipitate formed. Filtration, extensive washing with water and drying yielded 23.7 g. (64.9% based on 2-bromodibenzofuran) of 2-dibenzofurancarboxylic acid, m.p. range 245-253°. Recrystallization of this material gave 17.2 g. of white needles, m.p. 253-255°. From the mother liquors of the recrystallization were recovered 1.70 g. of less pure acid, m.p. range 249-255°.

The infrared spectrum of the acid possessed an absorption band at 5.98μ due to the carbonyl group.

Preparation of 2-dibenzofurancarboxamide

Hydration of 2-cyanodibenzofuran. The preparation of the amide of 2-dibenzofurancarboxylic acid was accomplished a number of years ago by Kirkpatrick;[110] however, no report of this compound has appeared in the literature to date.

Method 1. The following procedure was suggested by the report[113] that 2,3,6,7-tetramethylnaphthalene-1,4-dinitrile was converted to the corresponding dicarboxamide in 97% yield on treatment with potassium hydroxide in ethylene glycol-water.

A suspension of 0.50 g. (0.0026 mole) of 2-cyanodibenzofuran in 40 ml. of ethylene glycol and 5 ml. of water in which 4.0 g. of potassium hydroxide had been dissolved was heated at reflux for six hours. The evolution of ammonia from the reaction mixture was detected by odor one hour after the reaction was begun. Acidification of the light yellow solution following filtration yielded a white precipitate, 0.51 g., m.p. range 250-256°. Recrystallization from glacial acetic acid gave 0.40 g., of 2-dibenzofurancarboxylic acid, m.p. 253-256°.

After the failure of this reaction to yield the desired amide, it was noted that Mosby[113] did not report an analysis

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[113] W. L. Mosby, ibid., 75, 3600 (1953).

for his alleged dicarboxamide, a qualitative test for nitrogen apparently was not carried out and the product had a m.p. (>320°) which seems rather high for the compound reported. It is suggested that hydrolysis rather than hydration occurred in his case also.

Method 2. This procedure was based on the method employed for the hydration of o-tolunitrile to o-toluamide.[114]

A slurry of 1.93 g. (0.01 mole) of 2-cyanodibenzofuran in a solution of 0.1 g. of sodium hydroxide in 100 ml. of ethanol was prepared. Forty ml. of three per cent hydrogen peroxide were added with stirring, whereupon the temperature of the reaction mixture rose from 26° to 31°. The reaction mixture was heated to 50° and stirred at this temperature for three hours. After the solution had cooled to room temperature, it was just neutralized with sulfuric acid and poured into a large volume of water. The white amorphous product, 1.97 g. by weight, melted over the range 130-203°. Recrystallization from ethanol gave 0.91 g. (43.1%) of 2-dibenzofurancarboxamide, m.p. range 215-221°, soft at 208°. A second recrystallization from ethanol raised the m.p. to 219.5-220.5°.

The infrared spectrum of the amide was characterized by -NH absorption bands at 2.98μ and 3.17μ and >C = O bands at 6.03μ and 6.17μ.

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[114] C. R. Noller in A. H. Blatt, "Organic Syntheses", Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 586.

Ammonolysis of 2-dibenzofurancarboxylic acid chloride. A suspension of 3.42 g. (0.0161 mole) of 2-dibenzofurancarboxylic acid in 22 ml. of thionyl chloride, 2 ml. of pyridine and 100 ml. of benzene (sodium dried) was refluxed for 7.5 hours. The excess thionyl chloride and benzene were removed by distillation, finally at aspirator vacuum. The light yellow residue was poured into 700 ml. of cold ammonium hydroxide. After 24 hours, the cream colored solid was filtered off, washed well with water and dried. The 3.12 g. represented a yield of 91.8%, m.p. 220-222°. Recrystallization from ethanol narrowed the melting point range to 220-221°. A mixed melting point with Kirkpatrick's sample[110] showed no depression.

Anal. Calcd. for $C_{13}H_9NO_2$: C, 73.92; H, 4.29; N, 6.63. Found: C, 73.79, 73.72; H, 4.18, 4.18; N, 6.72, 6.69.

Attempted reductions of 2-cyanodibenzofuran with lithium aluminum hydride

Method 1. An attempt was made to synthesize 2-dibenzofurancarboxaldehyde by reduction of the 2-nitrile according to the procedure suggested in the literature.[115-118]

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[115] L. Friedman, Abstracts 116th. Meeting, American Chemical Society, Atlantic City, N. J., 1949, p. 5M.

[116] A. L. Henne, R. L. Pelley and R. M. Alm, J. Am. Chem. Soc., 72, 3370 (1950).

[117] M. Yandik and A. A. Larsen, ibid., 73, 3534 (1951).

[118] L. I. Smith and E. R. Rogier, ibid., 73, 4047 (1951).

A suspension was made of 9.66 g. (0.05 mole) of 2-cyanodibenzofuran in 50 ml. of sodium-dried ether and 50 ml. of sodium-dried benzene. To the vigorously-stirred suspension was added 0.50 g. (0.013 mole, 0.25 equivalent + 5% excess) of lithium aluminum hydride in small portions. Almost immediately the suspension became orange-red in color. The reaction mixture was refluxed for 5.5 hours, then allowed to stand overnight. The excess lithium aluminum hydride was decomposed by addition of a 1:1 mixture of ethanol and anhydrous ether. The ether and alcohol were removed by distillation and the resulting reddish-brown suspension was heated with 100 ml. of benzene and filtered. The filtrate was washed with dil. hydrochloric acid, then with water, and was dried over anhydrous sodium sulfate. The benzene was removed by distillation, leaving 4.8 g. of residue, m.p. range 87-115°. This material was gummy in texture and had the odor of the original nitrile. Because of the lack of success in attempts to crystallize this substance, it was not further investigated.

Method 2. The reduction of the nitrile to the aldehyde is complicated by the fact that reduction of the -CN group leads to the formation of $-CH_2NH_2$ when excess hydride is present.[119-122] Accordingly, an attempt was made to synthesize the unknown 2-dibenzofurylmethylamine by reduction of 2-cyanodibenzofuran with excess lithium aluminum hydride.

A suspension of 1.04 g. (0.0273 mole) of lithium aluminum hydride in 100 ml. of sodium-dried ether was prepared. In a separatory funnel, 4.8 g. (0.0248 mole) of 2-cyanodibenzofuran was suspended in 50 ml. of dry benzene and 25 ml. of dry ether. The suspension of nitrile was added to the reducing agent at ice-bath temperature over a period of 45 minutes. A yellow coloration developed almost immediately. The reaction mixture was stirred at room temperature for six hours, then the excess hydride was decomposed with 100 ml. of wet ether, followed by 10 ml. of water and 100 ml. of 20% sodium hydroxide solution.

The emulsion which resulted was broken by the addition of a small amount of ethanol, and the ether-benzene layer was separated. The aqueous layer was extracted with both ether and benzene, and the combined extracts were dried over anhydrous

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[119] R. F. Nystrom and W. G. Brown, ibid., 70, 3738 (1948).

[120] L. H. Amundsen and L. S. Nelson, ibid., 73, 242 (1951).

[121] B. F. Crowe and F. F. Nord, J. Org. Chem., 15, 81 (1950).

[122] W. G. Brown in R. Adams, "Organic Reactions", Vol. 6, John Wiley and Sons, Inc., New York, N. Y., 1951, Chap. 10.

sodium sulfate. During the removal of the solvents by distillation, white needles precipitated. These needles were removed by filtration and found to weigh 0.21 g., with a melting range of 241° to 250° with decomposition. This material had a fishy odor; qualitative analysis indicated that nitrogen was present.

The infrared spectrum of this material possessed two bands of weak to moderate intensity at 3.70μ and 3.83μ in addition to a 1,2,4-substitution band of moderate intensity at 12.13μ.

The solution remaining after filtration of the white needles was heated on the steam bath until no more condensate was collected. The residue was dissolved (partly) in 150 ml. of dry ether and anhydrous hydrogen chloride was passed through the solution for one hour. The gummy reddish-brown precipitate which formed was filtered off and extracted with dry ether. The ether-insoluble material totaled 3.7 g., m.p. 100-115°.

The infrared spectrum of this material showed broad absorption bands at 3.70μ, 3.85μ and 4.10μ. The spectrum, though less sharp, was quite similar to that of the high-melting material previously isolated.

Bromination of 2-cyanodibenzofuran

To a solution of 9.7 g. (0.05 mole) of 2-cyanodibenzofuran in 150 ml. of glacial acetic acid were added 12 ml. (37.2 g., 0.23 mole) of bromine. The addition was done dropwise over a

period of 30 minutes at 70° with vigorous stirring. The resulting solution was refluxed for 4.5 hours. After 30 minutes a red precipitate appeared and after 80 minutes, the bromine color had completely disappeared. The reaction flask was cooled in an ice bath and the precipitate was filtered off and washed with cold glacial acetic acid. The 11.72 g. of steel gray plates were recrystallized from glacial acetic acid to give 3.3 g. of white plates, m.p. 277.5-278.5°. Concentration of the mother liquors gave an additional 2.0 g. of product, m.p. 275-276.5°. The 5.3 g. obtained represented a yield of 39.0% (calculated as a 2-cyano-x-bromodibenzofuran).

An analytical sample, m.p. 277.5-278.5°, of this material was prepared by recrystallization from glacial acetic acid.

The infrared spectrum of the supposed bromo-nitrile was very similar to that of 2-dibenzofurancarboxamide in that -NH bands were present at 3.01μ and 3.17μ and $>C=O$ bands at 6.04μ and 6.18μ. Also, there was no absorption characteristic of the $-C\equiv N$ in the region of 4.3μ - 5.3μ.

The compound gave a negative ferrox paper test[123] at room temperature and a faint positive test on heating. A negative hydroxamate test[124] for aromatic amides was obtained, but

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[123] D. Davidson, Ind. Eng. Chem., Anal. Ed., 12, 40 (1940).

[124] N. D. Cheronis and J. B. Entriken, "Semimicro Qualitative Organic Analysis", T. Y. Crowell Co., New York, N. Y., 1947, p. 130.

negative results were also obtained with benzamide and 2-dibenzofurancarboxamide.

Anal. Calcd. for $C_{13}H_8BrNO_2$: N, 4.83. Found: N, 3.84, 4.15.

The above analytical figures were obtained by a private laboratory. The writer obtained higher, albeit less precise, values for the nitrogen content, viz. 5.23%, 4.55% and 4.42%, the last determination being invalid because of leakage at the burette stopcock of the Dumas apparatus. Leakage of the potassium hydroxide solution at the stopcock would be expected to cause low results. The apparatus and writer's technique were checked by analysis of a pure sample of acetanilide. The percentage of nitrogen was found to be 10.45%; the calculated value is 10.37%.

The analytical values of the private laboratory suggest that a non-nitrogenous substance, presumably the bromo-acid, was present.

The writer's values, though differing by almost 0.7% (ignoring the lowest value), both lie within the permissible limits of deviation from the calculated value.

Hydrolysis of the supposed x-bromo-8-dibenzofurancarboxamide

To a solution of 20 g. of potassium hydroxide in 150 ml. of methanol were added 1.36 g. of the bromo-amide (?), and the mixture was refluxed for 43.5 hours. The solution was poured

into a large volume of water. This solution was filtered at its boiling point and acidified with hydrochloric acid. Filtration gave 1.25 g. of white amorphous solid, m.p. 332-335° with decomposition. Recrystallization of this material from glacial acetic acid yielded 0.70 g. of white needles, m.p. 334.5-336.5° with decomposition.

A melting point of 328° with decomposition has been reported[125] for 2-bromo-8-dibenzofurancarboxylic acid.

The infrared spectrum of the writer's preparation possessed a sharp band of high intensity at 6.00 μ due to the carboxyl group as well as substitution bands at 12.38 μ and 12.97 μ.

Ferrox paper tests with dibenzofuran compounds

In an effort to determine the nature of the product formed on bromination of 2-cyanodibenzofuran, the ferrox paper test[123] was applied to that substance. Because of the insolubility of the bromination product in the solvents used, no conclusive results were obtained. Table 7 contains the results of tests on some other dibenzofuran compounds. Where a test is listed as being performed "hot", warming in a burner flame is meant.

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[125] H. Gilman, P. T. Parker, J. C. Bailie and G. E. Brown, J. Am. Chem. Soc., 61, 2836 (1939).

Table 7

Ferrox Paper Tests for Oxygen

Compound	Solvent	Conditions	Results
---	benzene	room temp.	-
---	anisole	room temp., 2 min.	-
---	diphenyl ether	room temp., 12 hr.	-
		hot	+
hexadecanol-1	benzene	room temp.	+
benzamide	benzene (insol.)	room temp.	+
dibenzofuran	benzene	room temp.	-
	benzene	hot	-
	carbon tetrachloride	room temp.	-
2-dibenzofurancarboxamide	benzene (insol.)	room temp.	-
		hot	+
	carbon tetrachloride (insol.)	room temp.	-
	diphenyl ether (insol.)	room temp., 4 hr.	+
		hot	+
2-cyanodibenzofuran	diphenyl ether	room temp.	-
2-bromo-8-dibenzofurancarboxamide	benzene (insol.)	room temp.	-
		hot	+ (very faint)
	diphenyl ether	room temp.	-

Preparation of 2-bromo-8-dibenzofurancarboxamide

A mixture of 0.58 g. of 2-bromo-8-dibenzofurancarboxylic acid, 15 ml. of thionyl chloride, 35 ml. of sodium-dried benzene and one ml. of pyridine was refluxed for four hours. The benzene and excess thionyl chloride were removed at aspirator vacuum leaving a light yellow solid as residue. This solid was poured with stirring into 600 ml. of cold ammonium hydroxide. After nine hours, the mixture was filtered to give 0.50 g. (86.2%) of air-dried product, m.p. 273-276°. Attempted recrystallization from glacial acetic acid yielded needles having a lower melting point (271-274°). A mixed melting point determination with the product obtained from the bromination of 2-cyanodibenzofuran gave the range 269-274°.

Preparation of 2,8-dicyanodibenzofuran

The 2,8-dibromodibenzofuran used in this procedure was a student preparation which was recrystallized five times from large volumes of toluene to a melting point of 194-195°.

Fusion method. A mixture of 65.2 g. (0.200 mole) of 2,8-dibromodibenzofuran and 89.6 g. (0.500 mole as the dimer) of cuprous cyanide was heated at 270° with constant stirring for 4.5 hours. At this point the reaction mixture which had been liquid suddenly solidified, stopping the stirrer. The mixture did not remelt at 300°. The solid was removed from the flask

and ground thoroughly in a mortar. The black powder was extracted for 48 hours with benzene. On evaporation of the solvent, 6.87 g. of white needles were obtained, m.p. 302.5-305°. Recrystallization from benzonitrile gave 5.48 g. (12.5%) of needles, m.p. 302-304°. Another recrystallization, this time from benzonitrilebenzene (4:1), and vacuum sublimation raised the melting point of the long white needles to 304-305°.

In the infrared spectrum, a -CN band was present at 4.47μ and a 1,2,4-substitution band at 12.07μ.

Shortly after this preparation had been completed, Moffatt[67] reported the synthesis of 2,8-dicyanodibenzofuran, m.p. 299°. Dr. Moffatt kindly supplied the writer with a sample of his preparation. His sample was found to melt at 304°, and a mixed melting point with a sample prepared by the writer showed no depression.

Quinoline as solvent. A mixture of 8.4 g. (0.0258 mole) of 2,8-dibromodibenzofuran, 12.0 g. (0.067 mole as dimer) of cuprous cyanide and 50 ml. of quinoline was heated at 175° for 24 hours with vigorous stirring. The reaction mixture was worked up by the usual treatment with acid to give 7.7 g. of dark brown material. Extraction of this substance with benzene for 20 hours gave 2.29 g. (40.7%) of gray powder, m.p. range 270-285°. Two recrystallizations from glacial acetic acid raised the melting point to 304-305°.

Hydrolysis of 2,8-dicyanodibenzofuran

A solution of 2.00 g. (0.00917 mole) of the dinitrile and 100 g. of potassium hydroxide in 275 ml. of methanol was refluxed for 23 hours. At the end of this period, the mushy white mass of potassium salt was dissolved by the addition of a small amount of water, and after the addition of Norit A the mixture was filtered at its boiling point. On acidification with hydrochloric acid, 2,8-dibenzofurandicarboxylic acid precipitated. Filtration and drying yielded 2.28 g. (97.0%) of white amorphous powder subliming at 440-442° after darkening at 400°. Unsuccessful attempts were made to recrystallize this acid from acetic acid and from ethanol.

A number of references to 2,8-dibenzofurandicarboxylic acid are to be found in the literature,[126-128] but no melting point has been reported for this compound to date.

Bromination of 3-nitrodibenzofuran[107]

A solution of 20.0 g. (0.0938 mole) of 3-nitrodibenzofuran[129] (m.p. 181.5°) in 400 ml. of glacial acetic acid was

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[126] Y. Sugii and T. Sengoku, J. Pharm. Soc. Japan, 53, 951 (1933) /C. A., 29, 5444 (1935)/.

[127] M. Tomita, ibid., 56, 906 (1936) /C. A., 31, 3484 (1937)/.

[128] H. Gilman, H. B. Willis and J. Swislowsky, J. Am. Chem. Soc., 61, 1371 (1939).

[129] Sample kindly supplied by Mr. R. K. Ingham.

prepared and heated to 80°, whereupon 22 ml. (68.2 g., 0.426 mole) of bromine was added over a period of 1.5 hour to the well-stirred solution. The reaction mixture was refluxed for nine hours. At the end of this time the bromine color had been discharged, and a cream-colored suspension was present. After cooling of the reaction mixture to room temperature, the solid material was filtered off and dried. The crude product, m.p. 244-247°, was obtained in the amount of 23.3 g. (85.0%). Recrystallization from 2 l. of glacial acetic acid yielded 21.1 g. (77.0%) of white needles, m.p. 251.5-253°.

Using double the quantities employed above, a yield of 80.1% of pure bromo-nitro compound was obtained.

The infrared spectrum possessed absorption bands due to the nitro group at 6.57 μ and 7.45 μ and 1,2,4-substitution bands at 12.13 μ and 12.40 μ.

Preparation of 2-cyano-7-nitrodibenzofuran

Run 1. By the procedure described above (method 2) for the preparation of 2-cyanodibenzofuran, 12.0 g. of crude nitronitrile, m.p. range 226-230°, was obtained from 14.6 g. (0.05 mole) of 2-bromo-7-nitrodibenzofuran and 10.75 g. (0.06 mole as dimer) of cuprous cyanide in 100 ml. of quinoline. Recrystallization from glacial acetic acid raised the melting point of this material to 233-236°. Following vacuum sublimation at 0.2 mm. the melting point was 239-241°; two recrystallizations from glacial acetic acid gave needles melting at 247-249°. A

mixed melting point determination with 2-bromo-7-nitrodibenzofuran (m.p. 251.5-253°) produced the melting range 221-234°.

The infrared spectrum of this material showed a -CN absorption band at 4.50μ but absorption at 5.87μ characteristic of >C = O indicated that some hydration and/or hydrolysis had occurred.

Run 2. The same procedure and quantities of materials were used as in run 1; the crude material weighed 10.4 g. and melted over the range 210-218°. Extraction with benzene yielded 9.0 g. of brownish-black powder, m.p. range 218-223°. A 0.9 g. portion of this material was purified by chromotography from benzene solution on an alumina column and yielded 0.32 g. of white needles, m.p. 247-249°.

The analytical data for this compound have not been received as yet, but the infrared spectrum indicated that the compound was a nitro-nitrile. The -CN band was at 4.46μ and the nitro group absorbed at 6.53μ and 7.43μ. There was no evidence for the presence of a carbonyl group.

Hydrolysis of 2-cyano-7-nitrodibenzofuran

A mixture of 1.19 g. of crude 2-cyano-7-nitrodibenzofuran and 25 g. of potassium hydroxide in 175 ml. of methanol was refluxed for 48 hours. The slightly green suspension was poured into water, and the larger volume of suspension was heated to boiling and filtered. Acidification of the hot

filtrate yielded a brown floculent precipitate which proved to be insignificant on filtration.

One gram of brown solid had been retained on the filter paper. This material was heated to boiling with 100 ml. of 1:1 dil. hydrochloric acid giving 0.67 g. of brownish-green powder which did not melt at 400°.

The infrared spectrum indicated the presence of a carboxylate ion by absorption at 6.07μ. The nitro group absorbed weakly at 6.33μ.

Friedel-Crafts reaction of oxalyl chloride with dibenzofuran

A solution of 16.8 g. (0.100 mole) of dibenzofuran in 200 ml. of tetrachloroethane was prepared, and 22.3 g. (15.0 ml., 0.176 mole) of oxalyl chloride was added with vigorous stirring. The solution was cooled to 5°, and 31.0 g. (0.235 mole as monomer) of aluminum chloride was added in small portions over a period of 20 minutes. The temperature of the reaction mixture was maintained at 2-5° for four hours, then the reaction mixture was stirred at room temperature for 30.5 hours. Subsequent to hydrolysis, the tetrachloroethane was steam distilled and the residue was treated with a boiling aqueous solution of 40.0 g. of potassium hydroxide. Filtration and acidification gave a copious gelatinous precipitate. The dried material weighed 36.7 g. After 26 hours, boiling acetone had extracted 4.96 g. of white solid, m.p. range 243-249°, leaving residue. Recrystallization of this material from glacial

acetic acid gave 2.17 g. of product, m.p. range 243-251°. The infrared spectrum of this material was identical with that of an authentic sample of 2-dibenzofurancarboxylic acid. A second extraction with acetone for 60 hours gave 1.27 g. of tan amorphous substance, m.p. range 243-250°, leaving residue. The total of 6.23 g. of crude acid represented a yield of 29.4%.

Attempts to prepare the acid by the action of oxalyl chloride in nitrobenzene solution at 170° gave only a trace of alkali soluble material, m.p. range 185-195°, and the use of refluxing quinoline as solvent resulted in the formation of a black polymeric material.

Acetylation of dibenzofuran

Run 1. In accordance with the directions of Buu-Hoi,[130] 50.0 g. (0.297 mole) of dibenzofuran and 50 ml. (0.637 mole) of acetyl chloride were added to 150 ml. of thiophene-free benzene, and the solution was cooled to 0°. Vigorous stirring was commenced, and 50.0 g. (0.375 mole as monomer) of aluminum chloride was added in small portions. The color of the reaction mixture became successively yellow, orange and deep red. After four hours, the reaction mixture was hydrolyzed. Following steam distillation, the non-volatile material was extracted with benzene. Removal of the solvent by distillation gave 60.4

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[130] Ng. Ph. Buu-Hoi and R. Royer, Rec. trav. chim., 69, 861 (1950).

g. of brownish-yellow product, m.p. range 53-66°. The crude material was dissolved in benzene and chromatographed on an alumina column to give 12.7 g., m.p. range 63-67°; 24.3 g., m.p. 68-70°; 8.3 g., m.p. range 69-73.5°; 1.8 g., m.p. 70-73°; 0.6 g., m.p. range 70-75° and 3.1 g., m.p. 82-83°. The total amount of solid material recovered was 50.8 g. The melting point of the final fraction was not elevated by recrystallization from ethanol. The remainder of the crude 2-acetyl compound was not purified further but was used directly in the preparation of 2-dibenzofurancarboxylic acid (see below).

The infrared spectrum of 2-acetyldibenzofuran possessed absorption bands of high intensity at 5.98μ (>C = O) and 12.14μ (1,2,4-substitution).

Run 2. The solution of 168.2 g. (1.00 mole) of dibenzofuran, 129.3 g. (1.647 mole) of acetyl chloride and 160 g. (1.20 mole as monomer) of aluminum chloride was stirred for two hours at 0-10°, then at room temperature for 5.5 hours. After standing overnight, the reaction mixture was hydrolyzed. The benzene layer was separated, washed with water and sodium carbonate solution and dried over anhydrous calcium chloride. After removal of the benzene by distillation, the brown residue was divided into two approximately equal portions.

One portion (102.5 g. wet weight) of crude 2-acetyldibenzofuran was purified by distillation at aspirator vacuum. A colorless liquid (presumably acetophenone) distilled at 100°

at 13 mm. A white solid, m.p. range 65-75°, apparently dibenzofuran, distilled at 135-160° at 13 mm. The forerun totaled 45.0 g. The 2-acetyl compound distilled at 193-220° at 13 mm., chiefly at 210-220°. The 26.3 g. of material was recrystallized from ethanol-water to give 19.6 g. of white needles, m.p. 71-74°. A second recrystallization raised the m.p. to 72-75°.

The residue in the distillation flask weighed 16.5 g. and melted at 95-115°. It was not investigated further; probably this material was largely 2,8-diacetyldibenzofuran.

Repetition of the procedure used in run 2 on one-half the scale gave 61.5 g., b.p. range 152-160° at 0.16 mm., m.p. range 75-80°, soft at 65°. Recrystallization from ethanol was ineffective in purifying this material. An attempt to achieve separation by use of Girard's reagent[131] was unsuccessful also.

Haloform reaction with 2-acetyldibenzofuran

The general procedure used here was adapted from the directions[132] for the preparation of β-naphthoic acid from methyl β-naphthyl ketone.

A solution of potassium hypochlorite was prepared from 125 g. of "H.T.H.", 25 g. of potassium hydroxide and 82.5 g. of

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[131] A. Girard and G. Sandulesco, Helv. Chim. Acta, 19, 1095 (1936).

[132] M. S. Newman and H. L. Holmes in A. H. Blatt, op. cit., p. 428.

potassium carbonate. After filtration of the insoluble matter, the hypochlorite solution was heated to 55°, and 36.4 g. of crude 2-acetyldibenzofuran was added. The temperature was raised slowly to 100° at which point the reaction commenced, as evidenced by the refluxing of chloroform. The reaction mixture was cooled to 80°, where the temperature was maintained for 8.25 hours. The solution was treated with 40 g. of sodium bisulfite in 200 ml. of water to destroy excess hypochlorite. Enough potassium hydroxide was added to bring all material back into solution, and the solution was filtered at its boiling point. Acidification gave a white floculent precipitate which on filtration, washing and drying gave 45.3 g. (124%) of acid, m.p. range 235-247° with softening at 230°. Recrystallization from glacial acetic acid yielded 22.6 g. (61.6%) of 2-dibenzofurancarboxylic acid, m.p. range 250-254°.

In another run, 105.0 g. of crude 2-acetyldibenzofuran yielded 59.4 g. of crude 2-dibenzofurancarboxylic acid, m.p. range 225-245°. Recrystallization of this material from glacial acetic acid gave 36.4 g., m.p. 250-253°.

Esterification of 2-dibenzofurancarboxylic acid with methanol[133]

At a rapid rate, hydrogen chloride was passed into a well-stirred suspension of 43.8 g. (0.206 mole) of 2-dibenzofurancarboxylic acid in 1100 ml. of absolute methanol until all the

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[133]H. Gilman, W. Langham and H. B. Willis, J. Am. Chem. Soc., 62, 346 (1940).

acid had dissolved (three hours), then for one additional hour. Approximately 350 ml. of the methanol was removed by distillation, and the hot solution was filtered. On cooling 16.5 g. of methyl ester, m.p. range 77-81.5°, crystallized. The mother liquors were worked up to give additional crops: 12.3 g., m.p. 76-79° and 6.4 g., m.p. 71-74°. The 35.2 g. of ester were combined and recrystallized from methanol to give 26.6 g. (57.1%) of methyl 2-dibenzofurancarboxylate, m.p. 79.5-82°. A second recrystallization raised the melting point to 81.5-82.5°.

Carbonyl absorption was evident at 5.88μ in the infrared spectrum.

Preparation of 2-dibenzofurancarboxylic acid hydrazide

One and forty-three hundredths gram (0.0063 mole) of methyl 2-dibenzofurancarboxylate was added in small portions to a refluxing mixture of 25 ml. of hydrazine hydrate (95+%) and 50 ml. of ethanol. After completion of the addition, the reaction mixture was refluxed for five hours, then allowed to cool slowly to room temperature. Filtration and drying yielded 0.97 g. (67.7%) of white needles, m.p. 207-212° (Fisher-Johns block). Recrystallization from ethanol-water raised the m.p. to 210-212°.

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.14; H, 4.46; N, 12.38. Found: C, 68.99, 68.91; H, 4.51, 4.49; N, 12.49, 12.40.

The infrared spectrum of this compound showed an -NH band at 3.06μ and characteristic monosubstituted amide absorption

bands at 6.02 μ and 6.18 μ.

Repetition of this reaction with 11.3 g. of ester, 100 ml. of hydrazine hydrate and 500 ml. of methanol gave 8.5 g. (75.2%) of hydrazide, m.p. 208-211°.

Treatment of 2-dibenzofurancarboxylic acid hydrazide with benzenesulfonyl chloride

In accordance with the procedure of McFadyen and Stevens,[134] 4.52 g. (0.02 mole) of 2-dibenzofurancarboxylic acid hydrazide, 2.5 ml. (3.53 g., 0.02 mole) of benzenesulfonyl chloride and 100 ml. of pyridine were mixed, with ice-bath cooling. The yellow solution was stirred overnight, while the temperature of the reaction mixture was allowed to rise to room temperature. The solution was poured onto ice in hydrochloric acid. The pale yellow precipitate was removed by filtration, washed well with dilute hydrochloric acid and water and dried. The crude 2-dibenzofurancarboxylic acid benzenesulfonhydrazide melted at 217-220° (Fisher-Johns block) and weighed 6.45 g. (88.1%). An analytical sample prepared by recrystallization from ethanol melted at 220-221.5°.

Anal. Calcd. for $C_{19}H_{14}N_2O_4S$: C, 62.28; H, 3.85; N, 7.65; S, 8.75. Found: C, 62.24, 62.37; H, 3.98, 3.92; N, 7.71, 7.71; S, 8.65, 8.64.

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[134] J. S. McFadyen and T. S. Stevens, J. Chem. Soc., 584 (1936).

The infrared spectrum showed -NH bands at 3.02 μ and 3.18 μ, a monosubstituted amide band at 6.05 μ and a $-SO_2-$ band at 8.45 μ.

Preparation of 4-dibenzofurancarboxylic acid hydrazide

A solution of 2.26 g. (0.01 mole) of methyl 4-dibenzofurancarboxylate (m.p. 90-93°)[135] in 24 ml. of hydrazine hydrate (95+%) and 25 ml. of absolute ethanol was refluxed for eight hours, then cooled in the refrigerator. The long white needles which separated were collected by filtration and dried, giving 1.61 g. of crude product, m.p. 170-173°. The mother liquors yielded, on dilution to incipient turbidity at the boiling point, 0.24 g., m.p. range 167-171°. The overall yield was 1.85 g. or 81.9%. Two recrystallizations from ethanol yielded long silky needles having the melting point range of 171° to 175°. Forty-one hundredths gram of this material was dissolved in a mixture of 15 ml. of hydrazine hydrate (99-100%) and 15 ml. of absolute ethanol and the solution was refluxed overnight. Cooling gave 0.27 g. of needles, m.p. 172-174.5°. Recrystallization from absolute ethanol raised the m.p. to 174-175° (Fisher-Johns block). That this material was still impure was indicated by analysis.

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[135]This ester was prepared and generously supplied to the writer by Mr. K. Oita of This Laboratory.

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.14; H, 4.46; N, 12.38. Found: C, 68.69, 68.56; H, 4.58, 4.46; N, 12.66, 12.65.

Treatment of 4-dibenzofurancarboxylic acid hydrazide with benzenesulfonyl chloride

One gram (0.0044 mole) of 4-dibenzofurancarboxylic acid hydrazide (m.p. 171-173°) was treated with 1 ml. (1.38 g., 0.0078 mole) of benzenesulfonyl chloride in 100 ml. of pyridine in the manner described for the preparation of 2-dibenzofurancarboxylic acid benzenesulfonhydrazide. The crude product melted over a range from 235-240° with prior softening at 225°. Recrystallization from ethanol-benzene yielded 1.35 g. (83.3%) of short needles, m.p. 242-243°.

Anal. Calcd. for $C_{19}H_{14}N_2O_4S$: C, 62.28; H, 3.85; N, 7.65; S, 8.75. Found: C, 62.24, 62.22; H, 3.81, 3.85; N, 7.64, 7.65; S, 8.84, 8.76.

Preparation of 2-bromo-6-dibenzofurancarboxylic acid hydrazide

A solution of 3.05 g. (0.01 mole) of 2-bromo-6-carbomethoxydibenzofuran in 25 ml. of hydrazine hydrate (99-100%) and 65 ml. of ethanol was refluxed overnight and then allowed to cool slowly. Long white needles separated, m.p. 197-200.5°. The 2.40 g. of hydrazide obtained represented a yield of 78.7%. On recrystallization from absolute ethanol, the melting point was narrowed to 198-200°.

Anal. Calcd. for $C_{13}H_9BrN_2O_2$: Br, 26.16; N, 9.18. Found: Br, 25.87, 25.77; N, 9.14, 9.04.

Treatment of 2-bromo-6-dibenzofurancarboxylic acid hydrazide with benzenesulfonyl chloride

In the usual manner, 0.48 g. (0.0016 mole) of 2-bromo-6-dibenzofurancarboxylic acid hydrazide was treated with one ml. (1.38 g., 0.0078 mole) of benzenesulfonyl chloride in 100 ml. of pyridine. The yield of white amorphous powder was 0.54 g. (77.1%), m.p. 223-227°. An analytical sample of 2-bromo-6-dibenzofurancarboxylic acid benzenesulfonhydrazide obtained by recrystallization from aqueous ethanol melted at 228-229°.

Anal. Calcd. for $C_{19}H_{13}BrN_2O_4S$: Br, 17.95; S, 7.20. Found: Br, 17.74, 17.88; S, 6.95, 7.08.

Side chain bromination of 2-acetyldibenzofuran[30]

Method 1. A solution of 6.3 g. (0.03 mole) of 2-acetyldibenzofuran in 150 ml. of ether was cooled to 0°, and to it was added a solution of 4.8 g. (1.5 ml., 0.03 mole) of bromine over a period of five minutes. The solution was stirred for 4.25 hours at 0°, then allowed to stand overnight without stirring. The bromine color persisted throughout the manipulations. Removal of the ether on the steam bath left 7.8 g. of reddish-brown powder, m.p. range 72-76°. Recrystallization of the strongly lachramatory product from aqueous ethanol with the use of Norit A gave 2.57 g. of white crystals, m.p. range

90-95°. Two more recrystallizations from the same solvent yielded 1.10 g. (12.7%) of 2-(ω-bromoacetyl)dibenzofuran, m.p. 105.5-106.5° (Fisher-Johns block).

The infrared spectrum showed carbonyl absorption at 5.94μ and 1,2,4-substitution absorption at 12.42μ.

Repetition of the experiment using 150% of all quantities led to the isolation of 9.06 g. of white product, m.p. range 70-78°. Recrystallization from aqueous ethanol improved the purity only slightly (m.p. range 73-79°), therefore, the product was investigated via its infrared spectrum. There was no evidence for the presence of the desired bromo compound.

Method 2. To a solution of 6.7 g. (0.0314 mole) of 2-acetyldibenzofuran in 200 ml. of chloroform were added 15 drops of a solution of 6.24 g. (2.0 ml., 0.0390 mole) of bromine in 100 ml. of chloroform. Decolorization occurred almost immediately. Fifty ml. of the bromine in chloroform solution were added over a period of 15 minutes, and the solution was stirred vigorously for 70 minutes. The remainder of the bromine solution was added in 15 minutes and the reaction mixture was stirred for 24 hours at room temperature. After distillation of the chloroform, the residual reddish-brown gum was triturated with sodium bisulfite solution. The yield of 9.58 g., m.p. range 60-67°, amounted to 105.5% of theory. Four recrystallizations from dilute ethanol gave 0.75 g. (8.3%) of bromoacetyl compound, m.p. 103-105°.

Bromoacetylation of dibenzofuran

A solution of 168.2 g. (1.00 mole) of dibenzofuran in 600 ml. of nitrobenzene was prepared and cooled to 0°; 87.5 ml. (201.9 g., 1.00 mole) of bromoacetyl bromide was added over a period of 30 minutes. Then 160 g. (1.20 mole as monomer) of aluminum chloride was added in small portions over a period of one hour. The reaction mixture was stirred at room temperature for 24 hours, then hydrolyzed. The nitrobenzene was steam-distilled, and the residue was distilled at 13 mm. pressure. At 85-95°, nitrobenzene distilled. The distillation was stopped at 95° because of a red liquid which appeared at the side arm of the fractionating column.

At a bath temperature of 300°, nothing distilled at 1-2 mm. The residue in the distilling flask totaled 230 g., m.p. range 81-94°. Recrystallization from ethanol with the use of Norit A gave 109.0 g. of still impure product, m.p. range 96-103° and considerable tar. Two more recrystallizations from ethanol yielded 73.6 g. of brown needles, m.p. range 100-104°. A mixed melting point determination with the 2-(ω-bromoacetyl)-dibenzofuran showed considerable depression (m.p. range 92-99°). The infrared spectra of the two samples showed similarity, but not identity.

When an attempt was made to carry out the reaction in chloroform solution, complete polymerization occurred during the vacuum distillation of the product.

Based on the assumption that the product of the reaction described above was a mixture of 2-(ω-bromoacetyl)dibenzofuran and 2-(ω-chloroacetyl)dibenzofuran, an attempt was made to convert the chloroacetyl compound present to the bromo analogue.

The well-stirred suspension of 9.23 g. of the mixture (m.p. range 93-107°) and 20.2 g. of powdered potassium bromide in 500 ml. of dry acetone was refluxed for 72 hours. Removal of the acetone by distillation left 9.96 g., of white residue, m.p. range 88-92°. Recrystallization from absolute ethanol yielded 4.17 g., m.p. range 92-98°. A second recrystallization from the same solvent raised the melting point to 98-102°.

Chloroacetylation of dibenzofuran

A solution of 84.1 g. (0.50 mole) of dibenzofuran in 500 ml. of benzene was cooled to 0°, and 67.5 g. (45.0 ml., 0.60 mole) of chloroacetyl chloride were added rapidly. After aluminum chloride (100 g., 0.75 mole as monomer) was added over a period of 45 minutes, the dark viscous mixture was stirred for 24 hours, then hydrolyzed. The benzene layer was separated and dried over anhydrous calcium chloride. Distillation of the benzene left a solid possessing lachramatory properties. On distillation at aspirator vacuum, there was obtained 38.4 g. of a lachramator, presumably phenacyl chloride, b.p. range 125-130° at 13 mm. Vacuum pump distillation gave 59.2 g. of colorless liquid, b.p. range 205-209.5° at 1.2-2.0 mm., which

solidified in the receiver. This material had a melting point range of 93-102°. Recrystallization from benzene gave 30.36 g. of crude 2-(ω-chloroacetyl)dibenzofuran, m.p. 102-105.5°. Recrystallization from ethanol or benzene did not prove to be a satisfactory means of purification; chromatography gave as the best fraction, product melting over the range 101-108°.

When tetrachloroethane was used as solvent, a 0.4 mole run gave 112.4 g. of crude chloroacetyl compound. On attempted vacuum distillation, complete polymerization took place.

A 40% yield of 2-(ω-chloroacetyl)dibenzofuran, melting at 109-110°, has been reported.[30]

Haloform reaction with impure 2-(ω-bromoacetyl)dibenzofuran

A hypochlorite solution prepared from 25 g. of "H.T.H.", 17.5 g. of potassium carbonate and 5.0 g. of potassium hydroxide was heated to 60°, whereupon 11.6 g. of impure 2-(ω-bromoacetyl)dibenzofuran was added. The vigorously-stirred mixture was heated at reflux for three hours, then was filtered. Acidification of the filtrate gave a gelatinous precipitate which was filtered and dried. The 13.02 g. of white powder was recrystallized from glacial acetic acid (some material was insoluble) to give 3.69 g. of light yellow needles, melting at 312-316°, softening at 308°. The material gave a positive Beilstein test for halogen. Two other crops of needles were obtained on working up the insoluble material described above: 1.29 g., m.p. range 319-324° and 0.86 g., m.p. range 315-321°.

The three fractions were combined and recrystallized from glacial acetic acid to give 4.30 g., m.p. range 319-324°. A second recrystallization from the same solvent gave 3.67 g., m.p. 320-322.5°.

The infrared spectrum of this material possessed a sharp band of high intensity at 6.00μ (-COOH) and one of less intensity at 12.43μ (1,2,4-substitution). In practically all respects the spectrum was identical with that of the hydrolysis product of brominated 2-cyanodibenzofuran.

The analytical data, however, suggest that polyhalogenation may have occurred.

Anal. Calcd. for $C_{13}H_7ClO_3$: C, 63.30; H, 2.86; Cl, 14.38; neut. equiv. 246.6. Found: C, 59.85, 59.80; H, 2.70, 2.64; Cl, 18.61, 18.69; neut. equiv., 246.5, 250.7, 251.9.

Chlorination of 2-dibenzofurancarboxylic acid

To a hypochlorite solution prepared from 25 g. of "H.T.H.", 17.5 g. of potassium carbonate and 5.0 g. of potassium hydroxide were added 4.24 g. (0.020 mole) of 2-dibenzofurancarboxylic acid. The solution was stirred vigorously while the temperature was raised to 50° at which temperature 200 ml. of 1:1 hydrochloric acid were added over a period of 30 minutes. The reaction mixture which now contained precipitated material was heated for three hours at just below reflux temperature. Then 60 ml. of conc. hydrochloric acid were added rapidly, following which addition the mixture was stirred for an additional 3.5

hours. After the addition of a final 100 ml. of conc. hydrochloric acid, the reaction mixture was allowed to stand overnight. Filtration, washing with copious amounts of water and drying gave 3.17 g. of white powder, m.p. 288-291°, leaving residue. Three recrystallizations from glacial acetic acid yielded 1.03 g. of needles, m.p. range 309-315°.

The infrared spectrum of this material was identical with that of the substance obtained from the action of hypochlorite on bromoacetyldibenzofuran.

Decarboxylation of x-chloro-8-dibenzofurancarboxylic acid

In accordance with the procedure of Johnson and coworkers,[136] 0.99 g. of the supposed chloro-acid, 0.5 g. of copper powder and 10 ml. of quinoline were mixed in a six-inch Pyrex test tube fitted with an air condenser and suspended in a metal bath. The temperature of the bath was raised gradually to 250-255° and held there for 30 minutes. The mixture was allowed to cool, and the contents of the test tube were rinsed out with dil. hydrochloric acid, filtered, washed with water and dried. The dark brown powder was extracted twice with 100 ml. portions of methanol. Evaporation of the solvent left 0.48 g. of gray powder, m.p. range 70-85°. Recrystallization attempts using petroleum ether (b.p. range 60-70°), ethanol or

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[136] A. F. Shepard, N. R. Winslow and J. R. Johnson, J. Am. Chem. Soc., 52, 2083 (1930).

acetone-water did not prove successful. Vacuum sublimation at 70° and 0.006 mm. gave a small amount of white substance, melting at 60°, 76° and at 88°. This material possessed a fragrant odor, reminiscent of 2-bromodibenzofuran.

The infrared spectrum of the substance showed some similarity but not identity with that of an authentic sample of 2-chlorodibenzofuran.

Salt of hexamethylenetetramine with 2-(ω-bromoacetyl)dibenzofuran

Run 1. A suspension of 11.6 g. (0.040 mole) of 2-(ω-bromoacetyl)dibenzofuran, m.p. range 100-104°, and 5.60 g. (0.040 mole) of hexamethylenetetramine in 500 ml. of chloroform was stirred for 4.5 hours at room temperature and refluxed for two additional hours. After being cooled overnight in the refrigerator, the contents of the flask were filtered and the white product washed twice with chloroform, then with water and finally with ethanol. The 4.60 g. of white amorphous material formed a red melt at 158-161°. The original filtrate and washings were combined and worked up to yield an additional 4.46 g., m.p. range 166-170° with decomposition. The two crops represented a yield of 52.7%.

Run 2. The crude 2-(ω-bromoacetyl)dibenzofuran obtained from a 0.5 mole synthesis was employed directly without recrystallization. Treatment with 0.5 mole of hexamethylenetetramine

in one l. of chloroform gave 192.2 g. of crude quaternary salt, m.p. range 137-145° with decomposition.

Delepine reaction with hexamethylenetetramine salt of 2-(ω-bromoacetyl)dibenzofuran

Run 1. A suspension of 4.29 g. (0.01 mole) of the quaternary salt in 50 ml. of ethanol containing 5 ml. of conc. hydrochloric acid was stirred at room temperature for 21 hours. The finely divided white solid was filtered and washed with cold ethanol. The 3.49 g. of product melted at 258-261° with decomposition and leaving some residue (probably ammonium chloride).

Run 2. Repetition of the reaction with 4.46 g. of quaternary salt in 40 ml. of ethanol and 6 ml. of conc. hydrochloric acid gave 3.68 g. of product, m.p. 261-262° with decomposition.

The two yields were combined and washed free of inorganic salts with 100 ml. of water at 0°. The 3.72 g. of 2-(ω-aminoacetyl)dibenzofuran hydrochloride, m.p. 251-253° with decomposition represented a yield of 69.7% (based on 8.75 g. of starting material).

The infrared spectrum of the compound possessed a carbonyl band at 5.93μ and amine hydrochloride bands at 3.7μ and 3.8μ.

Run 3. When 104.2 g. of the quaternary salt melting over the range 137-145° was treated with 300 ml. of ethanol and 100 ml. of conc. hydrochloric acid, 74.2 g. of crude amine

hydrochloride was obtained, m.p. range 250-275° leaving residue. This material was stirred at room temperature with 300 ml. of water and 100 ml. of conc. hydrochloric acid, then cooled prior to filtration. The yield of 43.8 g., m.p. range 261-266° with decomposition, was 68.9% of theory.

Preparation of 2-(ω-acetamidoacetyl)dibenzofuran

Two ml. of acetic anhydride were added with vigorous stirring to a suspension of 1.31 g. (0.005 mole) of 2-(ω-aminoacetyl)dibenzofuran hydrochloride in 200 ml. of water. Immediately thereafter, a solution of 1.5 g. of sodium acetate in 15 ml. of water was added, and the reaction mixture was stirred for two hours at 10° and for eight hours at 25°. Filtration gave 1.30 g. of white amorphous powder, m.p. range 186-195°. Two recrystallizations from ethanol gave 0.48 g. (35.8%) of white needles, m.p. 192-193°.

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.84, 72.03; H, 5.01, 4.94; N, 5.22, 5.28.

Significant absorption bands in the infrared spectrum were at 2.97μ (-NH), 5.87μ and 6.10μ (>C = O) and 12.44μ (1,2,-4-substitution).

Preparation of 2-(ω-dichloroacetamidoacetyl)dibenzofuran

A suspension of 2.23 g. (0.0085 mole) of 2-(ω-aminoacetyl)dibenzofuran hydrochloride in 80 ml. of dry benzene was

treated with 1 ml. of dichloroacetyl chloride and the reaction mixture was refluxed for 12 hours. After three hours, all suspended material had gone into solution. On cooling, light tan needles precipitated. The 1.74 g. of product, m.p. range 160-165°, and 0.30 g., m.p. range 147-166°, of additional material obtained on concentration of the mother liquors were combined and recrystallized twice from benzene to give 1.12 g. (39.3%) of 2-(ω-dichloroacetamidoacetyl)dibenzofuran, m.p. 167-169°.

Anal. Calcd. for $C_{16}H_{11}Cl_2NO_3$: C, 57.16; H, 3.29; Cl, 21.09; N, 4.17. Found: C, 57.18, 57.17; H, 3.27, 3.28; Cl, 21.13, 21.02; N, 4.13, 4.15.

The infrared spectrum of the compound possessed an -NH absorption band at 3.04μ, and a carbonyl band at 6.02μ.

Hydroxymethylation of 2-(ω-acetamidoacetyl)dibenzofuran

A suspension of 12.85 g. (0.05 mole) of 2-(ω-acetamidoacetyl)dibenzofuran and 0.5 g. of sodium bicarbonate was prepared in 8.3 ml. of 37% formaldehyde solution and 100 ml. of ethanol. Though the reaction mixture was stirred overnight at 40°, complete solution never took place. The reaction mixture was filtered and the white product treated with hot benzene. Soluble material, isolated by concentration of the benzene extract, weighed 2.43 g. and melted over the range 135-165°. Evaporation of the remaining benzene left 2.66 g. of white powder, m.p. range 95-145°. The benzene insoluble material

weighed 5.94 g. and melted over the range 175-180°.

The reaction was repeated with the 11.03 g. of reaction product and the same amounts of formaldehyde, sodium bicarbonate and ethanol as used previously.

The infrared spectrum did not indicate that any hydroxymethyl compound was formed.

Bromoacetylation of 3-nitrodibenzofuran

The suspension of 53.3 g. (0.25 mole) of 3-nitrodibenzofuran in 500 ml. of nitrobenzene was stirred vigorously while 26.3 ml. (60.6 g., 0.30 mole) of bromoacetylbromide were added rapidly. The reaction flask was cooled to 0° while 48.0 g. (0.36 mole as monomer) of aluminum chloride were added. The suspension became orange, red, then deep scarlet. After being stirred for 12 hours at room temperature, the reaction mixture was hydrolyzed, then steam distilled. The non-volatile material was triturated with methanol then dried thoroughly. The brown powder, which weighed 67.9 g., melted over the range 120-159°. Recrystallization from glacial acetic acid was attempted, but the substance proved to be quite insoluble in this solvent. After the acetic acid treatment, the melting point range was 200-220° with softening at 180°. The material was divided into three portions, each of which was extracted with acetone for 24 hours. The insolubility of the substance precluded complete extraction of the supposed bromoacetylnitrodibenzofuran. A total of 5.92 g. of needles was obtained

on cooling and filtering the extracts. The melting point ranges of the three crops were 227-230°, 220-228° and 226-228.5°. An analytical sample, m.p. 227-229° material, was prepared by vacuum sublimation at 190° and 1 mm.

Anal. Calcd. for $C_{14}H_8BrNO_4$: Br, 23.92; N, 4.11. Found: Br, 15.09, 15.09; N, 4.82, 4.81.

The material not extracted by acetone totaled 29.17 g. The three crops had melting point ranges of 226-230°, 226-229° and 222-228°.

The infrared spectrum indicated a carbonyl group (5.92μ), nitro group (6.57μ and 7.47μ) and 1,2,4-substitution (12.30μ).

Oxidation of 2-(ω-bromoacetyl)-7-nitrodibenzofuran

A mixture of 2.00 g. of the supposed 2-bromoacetyl-7-nitrodibenzofuran was treated with a hypochlorite solution prepared from 10 g. of "H.T.H.", 8 g. of potassium carbonate and 2 g. of potassium hydroxide. After six hours of refluxing Norit A was added, and the mixture was filtered. Acidification gave 1.39 g. of green material, m.p. range 320-325° softening at 280°. Three recrystallizations from glacial acetic acid gave 0.47 g. of 3-nitro-8-dibenzofurancarboxylic acid, m.p. range 310-325°. A decomposition point of 300° has been reported for this compound.[125]

Salt of 2-(ω-bromoacetyl)-7-nitrodibenzofuran with hexamethylenetetramine

A mixture of 2.0 g. (0.006 mole) of 2-bromoacetyl-7-nitrodibenzofuran and 0.84 g. (0.006 mole) of hexamethylenetetramine in 250 ml. of chloroform was refluxed for 24 hours. After cooling, the white precipitate was filtered off. Filtration and drying yielded 0.99 g. of salt, m.p. range 176-180° with decomposition.

When a refluxing period of two hours followed eight hours stirring at room temperature, 1.63 g. of salt was obtained, m.p. range 205-215° with decomposition.

Delepine reaction with hexamethylenetetramine salt of 2-(ω-bromoacetyl)-7-nitrodibenzofuran

A suspension of 0.99 g. of the quaternary salt (m.p. range 176-180°) in 10 ml. of conc. hydrochloric acid and 50 ml. of ethanol was stirred for 24 hours at room temperature. The light brown product weighed 0.36 g. and melted over a range of 280-290° leaving a residue.

Preparation of 2-(ω-acetamidoacetyl)-7-nitrodibenzofuran

The 0.36 g. of 2-(ω-aminoacetyl)-7-nitrodibenzofuran hydrochloride was stirred with 2 ml. of acetic anhydride in 100 ml. of water to which 1.0 g. of sodium acetate had been added. After 12 hours, the white amorphous material was filtered off.

Twenty-three hundredths gram of product, m.p. range 219-225°, was recrystallized from glacial acetic acid. The melting point range was lowered to 213-220°. Vacuum sublimation at 210° at 0.001-0.005 mm. yielded a small amount of brown substance, m.p. range 205-213°.

Benzoylation of dibenzofuran

Run 1. In an attempted duplication of the results of Willis,[17] 43.7 g. (0.26 mole) of dibenzofuran were dissolved in 400 ml. of nitrobenzene and 53.0 g. (0.40 mole as monomer) of aluminum chloride were added. With vigorous stirring, 59.0 g. (48.7 ml., 0.42 mole) of benzoyl chloride were added slowly. The dark reddish-brown solution was allowed to stir for 14 hours at room temperature prior to hydrolysis. The nitrobenzene layer was steam distilled, the residue solidifying on cooling. This material which weighed 85.3 g. and melted over the range 96-124° was pulverized, then washed with a 5% solution of sodium hydroxide. After washing with methanol, the product weighed 76.8 g. and melted from 110° to 128°. Recrystallization from ethanol-benzene gave 40.2 g. of plates, m.p. range 127-134°, softening at 110°. The use of glacial acetic acid as a recrystallization solvent gave 30.8 g., m.p. 130-136°, softening at 115°. Two more recrystallizations from glacial acetic acid failed to raise the melting point. Chromatography and the recrystallization from acetic acid of fractions melting above 130°

gave 28.18 g. (39.8%) of white needles, m.p. 134-137.5°. Recrystallization of a sample for analysis raised the melting point to 136° to 138°.

This material analyzed correctly for a benzoyldibenzofuran. Willis[17] has reported a melting point of 135-136° for 2-benzoyldibenzofuran.

Anal. Calcd. for $C_{19}H_{12}O_2$: C, 83.80; H, 4.44. Found: C, 83.72, 83.72; H, 4.50, 4.56.

The infrared spectrum of the ketone had a carbonyl absorption band at 6.08μ and a 1,2,4-substitution band at 12.18μ.

The filtrate from the recrystallization of the material (m.p. 110-128°) was worked up to give tan plates, m.p. range 97-115°. Two recrystallizations from glacial acetic acid gave 2.94 g. (3.0%) of plates, m.p. 167-168.5°. This fraction analyzed correctly for a dibenzoyldibenzofuran.

Anal. Calcd. for $C_{26}H_{16}O_3$: C, 82.96; H, 4.29. Found: C, 82.71, 82.80; H, 4.40, 4.34.

In the infrared spectrum, carbonyl group absorption took place at 6.06μ and the 1,2,4-substitution band was located at 12.03μ.

Run 2. The same quantities of reactants were employed as in run 1 except that only 36 ml. (43.9 g., 0.31 mole) of benzoyl chloride were used. The reaction was carried out as before; however, following steam distillation of the solvent the residue was dried, then vacuum distilled. Over a range of 180-186° at

0.05 mm., 52.9 g. of 2-benzoyldibenzofuran distilled. Recrystallization of this crude ketone, m.p. range 123-134°, from acetic acid-water gave 46.5 g. of white needles, m.p. range 130-137° softening at 116°. A recrystallization from glacial acetic acid gave 31.34 g. (37.1%) of needles, m.p. 136-138°.

Dibenzoylation of dibenzofuran

To a solution of 43.7 g. (0.26 mole) of dibenzofuran in 450 ml. of nitrobenzene were added 98.0 ml. (119.6 g., 0.85 mole) of benzoyl chloride and 106.0 g. (0.79 mole as monomer) of aluminum chloride. The reaction mixture was stirred at room temperature for 18 hours; hydrolysis followed by steam distillation yielded a red solid. After trituration with sodium hydroxide solution, the solid was recrystallized from acetic acid-water to give 41.71 g. of 2,8-dibenzoyldibenzofuran, m.p. range 150-163°. Recrystallization from glacial acetic acid gave 32.16 g. (32.8%) of diketone, m.p. 167-168.5°.

Preparation of 2-benzoyldibenzofuran oxime

A solution of 5.45 g. (0.020 mole) of 2-benzoyldibenzofuran and 1.53 g. (0.025 mole) of hydroxylamine hydrochloride in 150 ml. of ethanol and 20 ml. of pyridine was refluxed for nine hours. After dilution with a large volume of water, the white amorphous precipitate was filtered off, washed with a large amount of water and dried. The 5.88 g. of crude oxime was

heated for five hours in suspension in water. The purified oxime weighed 5.54 g. and melted over the range 151-158°. Recrystallization from ethanol-water gave 3.41 g. (59.3%) of white needles, m.p. 158-159.5°. An analytical sample prepared by recrystallization from ethanol had the same melting point.

Anal. Calcd. for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.55, 79.34; H, 4.57, 4.59; N, 4.94, 4.84.

The preparation of the oxime was also accomplished in sodium hydroxide solution and in sodium acetate solution in an effort to obtain the oxime of m.p. 182-183° reported by Willis.[17] No trace of the higher melting material was found.

The writer's sample of oxime possessed an -OH band at 3.1μ and a weak >C = N- band at 6.32μ. Willis' sample had these same bands, however, there were some differences in the 13-14μ region.

Preparation of 2-benzoyldibenzofuran hydrazone

Method 1. A solution of 2.72 g. (0.01 mole) of 2-benzoyldibenzofuran in 1.0 ml. (1.0 g., 0.02 mole) of hydrazine hydrate and 65 ml. of ethanol was refluxed for 3.5 hours, then cooled in the refrigerator. The 2.19 g. of long transparent needles melted over the range 135° to 139°. Repetition of the reaction with this material and 10 ml. of hydrazine hydrate gave 1.31 g. of needles, m.p. range 125-140°, softening at 120°.

The infrared spectrum of these needles was identical with that of 2-benzoyldibenzofuran.

Method 2. In accordance with the procedure of Szmant and McGinnis,[137] a solution of 1.31 g. (from method 1) of 2-benzoyldibenzofuran in 10 ml. of hydrazine hydrate and 250 ml. of ethanol was refluxed for 47 hours in a Soxhlet extractor, the thimble of which contained 40 g. of freshly heated calcium oxide. The solution was concentrated to 100 ml., filtered, and water was added to incipient turbidity. The material recovered by filtration weighed 1.20 g. and melted at 95-110°. Two recrystallizations from ethanol containing a small amount of hydrazine hydrate gave 0.58 g. of plates, m.p. range 137-143° softening at 132°. This material became deep yellow in color after several weeks.

The infrared spectrum of this material differed from that of the ketone in the absence of the carbonyl absorption band. The weak band at 6.40μ may be due to the $\geq C = N-$ linkage, and a broad but weak band at 3.0-3.1μ may indicate -NH absorption.

Beckman rearrangement of 2-benzoyldibenzofuran oxime

To a solution of 2.87 g. (0.01 mole) of 2-benzoyldibenzofuran oxime in 200 ml. of dry benzene was added 3.12 g. (0.015 mole) of phosphorus pentachloride. The now green solution was

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[137]H. H. Szmant and C. McGinnis, ibid., 72, 2890 (1950).

stirred at room temperature for 12 hours. Subsequent to hydrolysis, the benzene layer was separated and washed with sodium carbonate solution. Evaporation of the benzene left 2.81 g. (98.0%) of a pink powder, m.p. range 160-164°. Two recrystallizations from ethanol raised the melting point to 164-165.5°. A mixed melting point determination with the original oxime gave the range 128-164°.

Anal. Calcd. for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.39, 79.48; H, 4.44, 4.45; N, 4.99, 4.96.

The infrared spectrum showed -NH band at 3.1μ and a carbonyl band at 6.10μ.

Hydrolysis of rearrangement product of 2-benzoyldibenzofuran oxime

A solution of 1.00 g. of amide in 20 ml. of conc. sulfuric acid, 50 ml. of glacial acetic acid and 80 ml. of water was refluxed for eight hours. The reaction mixture was poured onto ice, and the floculent white precipitate was filtered to give 0.59 g. of acid, m.p. range 220-240° with softening at 190°. The filtrate evolved the odor of aniline on being made alkaline. The solid acid was dissolved in sodium hydroxide solution from which it was reprecipitated (after filtration) by acidification. The 0.43 g. of acid melted over a range of 235-245°. Two recrystallizations from glacial acetic acid gave needles, m.p. 252-255°. There was no depression of melting point with an

authentic sample of 2-dibenzofurancarboxylic acid.

This amide was thus proven to be 2-dibenzofurancarboxylic acid anilide. Attempts to prepare this anilide from 2-dibenzofurancarboxylic acid chloride and aniline proved unsuccessful.

Benzoylation of 2-aminodibenzofuran

A reaction mixture consisting of 1.83 g. (0.01 mole) of 2-aminodibenzofuran, 3 ml. of benzoyl chloride and 0.5 g. of sodium hydroxide in 100 ml. of water was stirred for 10 hours. The suspended material was filtered off and washed thoroughly with warm dil. hydrochloric acid. The 1.94 g. (67.6%) of crude amide had a melting point range of 178-183°. Two recrystallizations from ethanol-water, followed by vacuum sublimation and another recrystallization from ethanol-water gave needles, m.p. 185-186°.

Anal. Calcd. for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.03, 79.08; H, 4.68, 4.62; N, 5.07, 5.05.

The infrared spectrum of the amide had an -NH band at 3.10μ and a $>C=O$ band at 6.09μ.

Preparation of 2,8-dibenzoyldibenzofuran dioxime

A solution of 3.76 g. (0.010 mole) of 2,8-dibenzoyldibenzofuran and 1.53 g. (0.022 mole) of hydroxylamine hydrochloride in 20 ml. of pyridine and 150 ml. of ethanol was refluxed for four hours, then poured into a large volume of water. The white precipitate was filtered and washed well with water. There was

obtained 4.03 g. (99.2%) of dioxime, m.p. 229° with decomposition. Recrystallization from a large volume of acetone gave 2.89 g. of fine white needles, m.p. 231.5-232° with decomposition.

Anal. Calcd. for $C_{26}H_{18}N_2O_3$: C, 76.84; H, 4.46; N, 6.89. Found: C, 76.57, 76.58; H, 4.61, 4.55; N, 6.74, 6.81.

The infrared spectrum of the dioxime showed a very weak >C = N- band at 6.30μ.

Two attempts to rearrange this dioxime by treatment with phosphorus pentachloride gave products melting over wide ranges which could not be recrystallized satisfactorily and which left residues on melting.

Dibenzoylation of 2,8-diaminodibenzofuran

A suspension of 1.98 g. (0.010 mole) of 2,8-diaminodibenzofuran and 1.2 g. (0.030 mole) of sodium hydroxide in 3.51 g. (2.9 ml., 0.025 mole) of benzoyl chloride and 100 ml. of water was stirred at room temperature for 3.5 hours. The solid material was filtered off and washed with warm dil. hydrochloric acid, then with copious amounts of water. The 2.12 g. of crude diamide, m.p. range 282-290°, were recrystallized from glacial acetic acid to give 1.30 g. of plates (32.0%), m.p. 293-296.5°. Recrystallization from glacial acetic acid, then from acetone-water, yielded transparent plates, m.p. 293-296°.

Anal. Calcd. for $C_{26}H_{18}N_2O_3$: C, 76.83; H, 4.46; N, 6.87. Found: C, 76.48, 76.56; H, 4.80, 4.72; N, 6.85, 6.92.

The infrared spectrum of the diamide showed -NH absorption at 3.1μ and >C = O absorption at 6.10μ.

Preparation of anilide of 4-dibenzofurancarboxylic acid

One gram (0.0047 mole) of 4-dibenzofurancarboxylic acid was suspended in a mixture of 5 ml. of thionyl chloride and 50 ml. of benzene. The reaction mixture was refluxed for 45 minutes, then 30 ml. of aniline in 50 ml. of benzene were added. Refluxing was continued for one hour. The mixture was poured into ice-hydrochloric acid and allowed to stand overnight. The benzene layer was separated and the solvent evaporated. The brown residue was washed successively with hydrochloric acid, water, dil. sodium hydroxide solution and again with water. The crude anilide weighing 1.21 g. (89.6%) melted over the range 140-150°. Recrystallization from ethanol-water, (twice), acetic acid-water and again from ethanol-water gave fine needles, m.p. 142.5-144.5°.

The infrared spectrum of the amide indicated some enolization by presence of >C = N band at 6.09μ in addition to >C = O absorption at 5.97μ.

Anal. Calcd. for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.35, 79.48; H, 4.53, 4.69; N, 5.02, 4.95.

Chlorination of dibenzofuran

In 600 ml. of glacial acetic acid were dissolved 8.4 g. (0.05 mole) of dibenzofuran, and the hypochlorite solution prepared from 50.0 g. of "H.T.H.", 35.0 g. of potassium carbonate and 10.0 g. of potassium hydroxide was added rapidly. Some dibenzofuran precipitated immediately. The reaction mixture was refluxed for ten hours. The light brown precipitate was filtered, washed and dried to give 13.8 g. of material, m.p. range 110-120°. Two recrystallizations from ethanol-water yielded fine white needles, m.p. 146-149° softening at 144°.

This material had an infrared spectrum identical with that of a compound reported by Oatfield[4] as being "probably a dichloro derivative of diphenylene oxide", m.p. 148°, softening at 144°. There was considerable difference from the spectrum of an authentic sample of 2,8-dichlorodibenzofuran.

A mixed melting point determination with Oatfield's sample (which was found to melt from 142° to 160° with residue melting at 175°) gave the range 147-155°.

Two additional recrystallizations of the writer's sample from ethanol-water raised the melting range to 155-160° with softening at 146°.

Attempted chloromethylation of dibenzofuran[7]

A solution of 84.0 g. (0.500 mole) of dibenzofuran in 300 ml. of glacial acetic acid was prepared, and 25.0 g. (0.277

mole) of trioxymethylene and 32.0 g. (0.235 mole) of freshly fused zinc chloride were added. Hydrogen chloride was passed at a rapid rate into the solution for 2.5 hours; during the first 1.5 hours the hydrogen chloride appeared to be completely absorbed. The reaction mixture was poured into 2 l. of ice water. A pink solid collected at the bottom of the beaker. This material was filtered and washed and dried as well as possible on a Buchner funnel. The oily solid was dissolved in ether, and the solution was washed with sodium carbonate solution and the extract dried over anhydrous calcium chloride. Removal of the ether on the steam bath left a reddish-purple solution which turned dark green on standing and evolved hydrogen chloride-like odors. The solution then solidified to a green glassy solid.

Distillation in vacuo gave 11.3 g. of dibenzofuran, b.p. 102° at 0.1 mm., m.p. 83°, mixed m.p., 82.5°.

The residue in the distillation flask could not be distilled at 0.05-0.10 mm. The dark green material was melted and poured out of the distilling flask. A light green powder (65.6 g., m.p. 92.5-93°) was obtained on pulverization. This polymeric material was insoluble in ether and ethanol, but soluble in benzene.

This polymeric material was obtained by Ingham[23] in his attempt to duplicate Kirkpatrick's[7] results.

A second trial of four-fifths the size of the first also gave only the green polymer in addition to unreacted dibenzofuran.

When an attempt was made to carry out the reaction in petroleum ether (b.p. 60-70°), only unreacted dibenzofuran was isolated.

Gattermann-Koch reactions

Preparation of p-tolualdehyde.[138] To 75 ml. (65.0 g., 0.705 mole) of toluene, previously dried over sodium, was added 9.7 g. (0.103 mole as CuCl) of cuprous chloride[139] and 86.7 g. (0.650 mole as monomer) of aluminum chloride.[140] Hydrogen chloride and carbon monoxide were bubbled through the reaction mixture for 3.5 hours, the former at the rate of two bubbles per second and the latter at half this rate.

After two hours, the mixture had thickened considerably. The reaction mixture was poured onto ice, then the organic layer was steam distilled until the distillate was no longer cloudy. To the distillate was added 100 ml. of ether and the two layers were separated. The aqueous layer was extracted several times

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[138] G. H. Coleman and D. Craig in A. H. Blatt, op. cit., p. 583.

[139] Baker and Adamson, Reagent Powder.

[140] Baker and Adamson, Reagent Grade, Anhydrous Sublimed.

with ether, and the extracts combined with the ether layer secured previously. The combined ethereal extracts were dried over anhydrous calcium chloride for 24 hours. The ether was removed by distillation from a steam bath and the residual oil was distilled.

Toluene (10 ml.) distilled at 107-119°, then p-tolualdehyde was collected in two fractions: b.p. range 190-201°, 5.95 g. and b.p. range 201-206°, 28.70 g. The yield of product, b.p. range 201-206°, was 39.8% based on the toluene actually used.

Attempted synthesis of 2-dibenzofurancarboxaldehyde.

Run 1. This experiment was based on the previous procedure for the preparation of p-tolualdehyde and Smith's[10] attempted preparation of 2-dibenzofurancarboxaldehyde.

At room temperature, hydrogen chloride and carbon monoxide at the rate of 1:2 were admitted to a solution of 33.65 g. (0.200 mole) of dibenzofuran, 26.67 g. (0.200 mole as monomer) and 3.00 g. (0.030 mole as monomer) of cuprous chloride in 100 ml. of nitrobenzene. The passage of the gases was continued for four hours, accompanied by stirring, though at no time did there appear to be absorption of the gases by the reaction mixture. The reaction mixture was hydrolyzed, then steam distilled until the distillate was no longer cloudy. The residue was a reddish-brown oil which solidified on cooling. This solid and the

supernatant liquid were extracted with ether several times. The ethereal extracts were combined, concentrated to 100 ml., then extracted with saturated sodium bisulfite solution. No aldehyde was obtained on acidification of this extract.

Run 2. This attempt was carried out with the same quantities of materials as before. However, while the gases were being admitted, the reaction flask was heated to 75-85° for five hours. Again, there appeared to be no absorption. After discontinuation of the heating and the flow of gases, the reaction mixture was allowed to stand for 24 hours. The reaction mixture was then hydrolyzed with ice and hydrochloric acid. The black tarry mass which settled out was subjected to steam distillation until a solid began to distill. The distillate was extracted several times with ether, and the combined extracts were dried over anhydrous calcium chloride. Removal of the ether and nitrobenzene by distillation left a residue which was identified as dibenzofuran by melting point and mixed melting point.

The residue from the steam distillation on extraction by ether in a Soxhlet extractor yielded 11.9 g. of material which gave a negative Schiff's test.

In another run, the reaction mixture (less the aluminum chloride) was heated to 70° before the aluminum chloride was added. Five minutes after this addition, the reaction mixture set to a black mass, which on close examination had the appearance of carbonized material.

Run 3. In 100 ml. of tetrachloroethane were suspended 33.65 g. (0.200 mole) of dibenzofuran and 6.0 g. (0.060 mole as monomer) of cuprous chloride. The reaction flask was cooled in an ice bath while 53.3 g. (0.200 mole as monomer) of aluminum bromide[141] was added.

The ice bath was removed and after the flask had warmed to room temperature, the passage of hydrogen chloride and carbon monoxide was begun. The temperature rose immediately but fell after 45 min. to 25°, the temperature maintained for the next five hours. The reaction mixture was deep purple in color. After steam distillation of the solvent, the residue was dried, then extracted with ether in a Soxhlet extractor. The 6.6 g. of material obtained gave a negative Schiff's test. A total of 31.3 g. of black tarry material was obtained. Evidently, the aluminum bromide exerted a high degree of carbonizing action on dibenzofuran.

Attempted preparation of 2-dibenzofurancarboxaldehyde by modified Gattermann reaction

Hinkel and co-workers[142] have reported the preparation of the desired aldehyde in 81% yield by means of Gattermann's aldehyde synthesis.

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[141]Sample generously supplied by Westvaco Chemical Division of Food Machinery and Chemical Corporation.

[142]L. E. Hinkel, E. E. Aylingand, J. H. Beynon, J. Chem. Soc., 778 (1937).

The writer preferred the generation of hydrogen cyanide *in situ*[143,144] to the use of liquid hydrogen cyanide.

To a solution of 67.3 g. (0.400 mole) of dibenzofuran in 200 ml. of tetrachloroethane were added 70.5 g. (0.600 mole) of zinc cyanide.[145] Hydrogen chloride was passed through the mixture for four hours. At this time all of the zinc salt appeared to have been decomposed. The reaction flask was cooled in an ice bath while 133.3 g. (1.00 mole as monomer) of aluminum chloride were added. The flow of hydrogen chloride was resumed and continued for eight hours, the reaction temperature being increased at the rate of 10° per hour to a final value of 80°.

The reaction mixture was hydrolyzed and the organic layer was steam distilled. The brown residue was ether extracted in a Soxhlet apparatus. The extracted material gave a negative Schiff's test.

Preparation of ethyl 2-dibenzofuranoxyacetate

In accordance with the procedure of Haskelberg,[146] 5.06 g. (0.0275 mole) of 2-hydroxydibenzofuran were dissolved in 45 ml.

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[143] R. Adams and I. Levine, J. Am. Chem. Soc., 45, 2373 (1923).

[144] R. Adams and E. Montgomery, ibid., 46, 1518 (1924).

[145] Schering-Kahlbaum product.

[146] L. Haskelberg, J. Org. Chem., 12, 426 (1947).

of ethanol and 0.64 g. (0.0278 g. atom) of sodium metal was added with ice-bath cooling. With vigorous stirring, 4.7 g. (3.1 ml., 0.0281 mole) of ethyl bromoacetate were added rapidly. The resulting dark brown solution was refluxed for three hours. The reaction mixture was cooled in an ice bath, but no product precipitated. The reaction mixture was poured into ice water, whereupon an oil formed. This oil solidified somewhat in the refrigerator. The sticky product was dissolved in ether and washed twice with dil. potassium hydroxide solution, then three times with water. After separation of the phases, the ether was evaporated to give 5.63 g. (75.6%) of ester, m.p. range 44-49°. Recrystallization from petroleum ether (b.p. range 40-50°) methanol gave long needles, m.p. 54-54.5° (Fisher-Johns block).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.13; H, 5.22. Found: C, 71.23, 71.14; H, 5.22, 5.30.

Methylation of 3-acetyl-4-hydroxydibenzofuran

One ml. of 50% sodium hydroxide solution was added to a refluxing solution of 1.00 g. (0.00442 mole) of 3-acetyl-4-hydroxydibenzofuran in 1 ml. of dimethyl sulfate and 35 ml. of acetone. After 11.5 hours, the suspension was poured into cold water and was placed in the refrigerator. Filtration gave a quantitative yield, m.p. 67-69.5°. Recrystallization from aqueous ethanol raised the melting point to 69.5-70.5°.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.98; H, 5.03. Found: C, 74.96, 75.07; H, 5.11, 5.03.

Miscellaneous Compounds

Condensation of chloroacetic acid with toluhydroquinone

A solution of 24.0 g. (0.194 mole) of toluhydroquinone,[147] 23.6 g. (0.250 mole) of chloroacetic acid and 20.0 g. (0.500 mole) of sodium hydroxide in 160 ml. of water was heated at reflux for 4.5 hours. The volume of solution was reduced by half by distillation and the semi-solid mass which remained was dissolved in the minimum amount of water. The alkaline solution was acidified to Congo Red with sulfuric acid, and the resulting mixture was cooled in an ice bath. The dark brown precipitate was removed by filtration and dried to give 27.6 g. of crude dioxyacetic acid, m.p. range 170-195°. Recrystallization from water yielded 11.4 g. of amorphous brown powder, m.p. range 195-208°. Two more recrystallizations from water raised the melting point to 212-213.5°. The 2.95 g. of product represented a yield of 6.3%. Due to an error in calculations, insufficient amounts of chloroacetic acid and base were used. Using proper quantities of these reagents it should be possible to obtain an improved yield of dioxyacetic acid.

Chlorination of 4-chlororesorcinol

A solution of 56.4 g. (0.39 mole) of 4-chlororesorcinol in 270 ml. of absolute ether was cooled to -2°, and 52.6 g. (0.39

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[147] Sample generously supplied by the Tennessee Eastman Corp.

mole) of sulfuryl chloride was added dropwise over a period of 30 minutes. The solution, now brown in color, was stirred for 16 hours, then the ether was removed by distillation. The white amorphous product which remained was recrystallized from petroleum ether (b.p. range 60-70°) to give 44.3 g. (63.5%) of white needles, m.p. 112.5-113.5°. The mother liquors yielded an additional 2.81 g. of 4,6-dichlororesorcinol, m.p. 112-113°.

Preparation of 4,6-dichlororesorcinoldioxyacetic acid

A solution of 47.2 g. (0.50 mole) of chloroacetic acid, 35.8 g. (0.20 mole) of 4,6-dichlororesorcinol and 36.0 g. (0.90 mole) of sodium hydroxide in 200 ml. of water was refluxed and stirred for 24 hours. The volume was reduced on the steam plate until crystallization commenced. After acidification with sulfuric acid, the brown suspension was cooled in an ice bath, filtered and washed with water. Thorough drying under the heat lamp gave 53.3 g. of brown powder possessing two melting point ranges, 164-167° and 181-194°.

The reaction was repeated with this crude material using the same quantities of the other reagents as above. After 20 hours of reflux, the mixture was worked up as before to give 48.1 g. only slightly purer material, m.p. ranges 165-169° and 206-210°. Recrystallization from hot water with decolorization by Norit A gave 21.48 g. (36.4%) of light tan needles, m.p. 226-228.5°.

Anal. Calcd. for $C_{10}H_8Cl_2O_6$: neut. equiv., 147.6. Found: neut. equiv., 147.4, 148.7.

Preparation of γ-(2,4-dichlorophenoxy)propyl chloride

To a solution of 7.1 g. (0.31 g. atom) of sodium metal in 200 ml. of absolute ether was added 80.0 g. (0.51 mole) of trimethylene chlorobromide and 50.0 g. (0.31 mole) of 2,4-dichlorophenol. The mixture was refluxed for three hours with stirring. The ethanol was distilled off on a steam bath, and 160 ml. of dry benzene was added. The solution was extracted three times with 100 ml. portions of 10% sodium hydroxide solution to remove unreacted phenol. The benzene extract was washed twice with 100 ml. portions of water, and the benzene layer was dried over anhydrous sodium sulfate. After 12 hours, the drying agent was filtered off, and the benzene was removed by distillation. The residue was fractionally distilled at aspirator vacuum to give 53.4 g. (71.9%) of γ-(2,4-dichlorophenoxy)propyl chloride, b.p. 166-168° at 15 mm.

A boiling point of 185-187° at 34 mm. and a yield of 78% have been reported by Synerholm and Zimmerman.[148]

Repetition of the experiment on double this scale gave a poorer yield (55.2%) of less pure product (b.p. range 165-170° at 14.5 mm.).

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[148] M. E. Synerholm and P. W. Zimmerman, Contrib. Boyce Thompson Inst., 14, 369 (1947) [C. A., 41, 4132 (1947)].

Preparation of δ-(2,4-dichlorophenoxy)valeric acid

To a solution of 3.6 g. (0.156 g. atom) of sodium metal in 75 ml. of absolute ethanol was added 25.0 g. (0.156 mole) of diethyl malonate and 37.5 g. of γ-(2,4-dichlorophenoxy)propyl chloride. The reaction mixture was stirred and refluxed for five hours. After the alcohol had been removed by distillation, the residual material was dissolved in 100 ml. of benzene, washed twice with 50 ml. portions of water and dried over anhydrous sodium sulfate for 12 hours.

Attempted vacuum distillation of the di-ester was unsuccessful; the pressure within the system increased steadily due perhaps to decomposition of the di-ester. The crude ester was dissolved in 175 ml. of ethanol and 50 ml. of 40% sodium hydroxide were added. This mixture was heated to reflux for 1.5 hours, then diluted with 800 ml. of water. The resulting suspension was extracted with benzene to remove excess aryloxyalkyl halide, and the aqueous layer was separated and acidified with dilute sulfuric acid. The acidic mixture was extracted with benzene and this extract was dried over anhydrous sodium sulfate. The benzene was removed by distillation at aspirator vacuum. The residual oil, presumably the substituted malonic acid, was heated at 240-250° (Wood's metal bath) for one hour. The resulting oil was vacuum distilled. Two fractions were collected: 120-180° and 180-182°, both at 0.2 mm. The second fraction, a viscous light green oil, solidified completely

after standing for 72 hours in the refrigerator.

A yield of 8.44 g. (20.6% based on the substituted propyl chloride) of light yellow crystals, m.p. 61-64°, was obtained. After recrystallization from carbon tetrachloride, a sample prepared for testing melted at 70-71°. The reported[148] melting point for this compound is 65°.

Preparation of β-(2,4-dichlorophenoxy)ethyl chloride

Seven and one-tenths grams (0.31 g. atom) of sodium metal was dissolved in 200 ml. of absolute ethanol and 50.0 g. (0.31 mole) of 2,4-dichlorophenol and 73.1 g. (0.51 mole) of ethylene chlorobromide were added. After 14 hours refluxing, the alcohol was removed by distillation and 150 ml. of dry benzene were added. After extraction of the benzene solution with three 75 ml. portions of 10% sodium hydroxide solution, the benzene layer was washed with water and dried overnight over anhydrous sodium sulfate. Distillation of the crude product gave 38.1 g. (54.5%) of β-(2,4-dichlorophenoxy)ethyl chloride,[149] b.p. 155.5-156.5° at 16.5 mm. The residue in the distillation flask solidified on cooling. One recrystallization of the white needles from ethanol gave 1.6 g. of compound, m.p. range 128-132°. A second recrystallization from ethanol raised the melting point to 132-133.5°. Presumably, this

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[149] The reported boiling point for this compound is 134-135° at 5.5 mm. U. S. Patent 2,186,367 /C. A., 34, 3281 (1940)/.

compound is bis-1,2-(2,4-dichlorophenoxy)ethane which is reported to melt at 132-133°.[150] Repetition of the experiment using 150% of the quantities employed above gave a 24.1% yield of aryloxyalkyl chloride, b.p. range 151-157° (chiefly at 152-154°) at 12 mm. The residue of 3.25 g. melted at 133.5-134.5° after two recrystallizations from ethanol.

Preparation of β-(2,4-dichlorophenoxy)ethylmalonic acid

To a solution of sodium ethoxide prepared from 2.9 g. (0.125 g. atom) of sodium metal and 100 ml. of absolute ethanol was added 20.0 g. (0.125 mole) of diethyl malonate and 28.2 g. (0.125 mole) of β-(2,4-dichlorophenoxy)ethyl chloride. After the reaction mixture had been refluxed for 6.25 hours, a solution of 30.0 g. of sodium hydroxide in 40 ml. of water was added. The refluxing was continued for an additional 3.3 hours after this addition. Subsequent to dilution with a large volume of water, the mixture was extracted with benzene. The aqueous layer was separated and acidified with sulfuric acid. Benzene extraction was followed by drying of the benzene solution over anhydrous sodium sulfate. The benzene was removed by distillation at aspirator vacuum, leaving a residue of light brown crystals and an oil phenolic in odor. The entire residue was taken up in sodium hydroxide solution and extracted with

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[150] U. S. Patent 2,130,990 [C. A., 32, 9098 (1938)].

benzene. The aqueous layer was separated, acidified and placed in the refrigerator. After 48 hours, a brown oil which had settled out solidified. Filtration and drying yielded 0.85 g. of a cream-colored solid, m.p. range 115-126° with gas evolution. Dissolution in alkali, filtration and acidification in the cold gave 0.63 g. (1.7%) of acid, m.p. 125-128° with softening at 123° and evolution of gas at the melting point.

This compound has not been analyzed; an insufficient amount remained after most of the sample was submitted for phytohormonal testing.

DISCUSSION

Preparative Methods

A compound which has shown potent antibacterial activity is 5-nitro-2-furaldehyde semicarbazone (Furacin).[151]

The steps leading to the synthesis of the corresponding dibenzofuran compound appeared worthy of investigation.

Actually only the 1,4-disubstituted dibenzofuran would preserve the *para* relationship between substituents. However, there is no evidence to indicate that this orientation of substituents is critical in the dibenzofuran analogue.[152]

Accordingly, a study was made of the preparative methods for the intermediates in the synthesis of 3-nitro-8-dibenzofurancarboxaldehyde semicarbazone. This isomer appeared to be the most accessible one because of the ease of preparation of 2-bromo-7-nitrodibenzofuran.

Several reaction sequences suggested themselves immediately.

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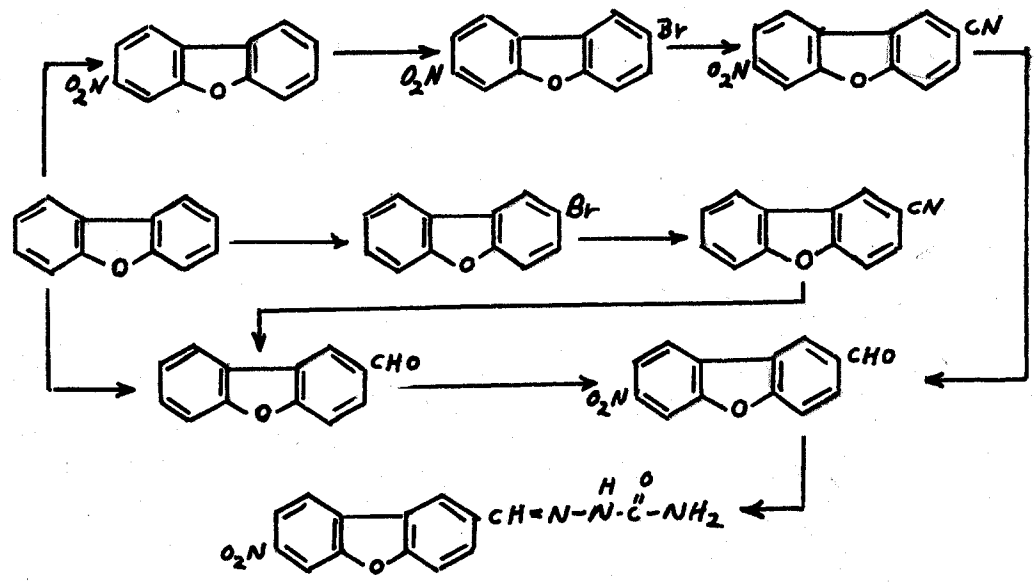
[151] G. L. Jenkins and W. H. Hartung, "The Chemistry of Organic Medicinal Products", John Wiley and Sons, Inc., New York, N. Y., 3rd ed., 1949, p. 513.

[152] In the furan series, Furacin is much more active than the semicarbazone of 2-nitro-4-furaldehyde. K. Hayes, *J. Am. Chem. Soc.*, 71, 2581 (1949).



Initially, the scheme involving formation of the aldehyde and its nitration as the diacetate appeared most attractive.

Experimentation did not reach this point, however; the stumbling block was the failure of many experiments to yield the desired 2-dibenzofurancarboxaldehyde.

Though the Gattermann synthesis of 2-dibenzofurancarboxaldehyde has been reported,[142] an attempt to repeat the synthesis (using a modified Gattermann reaction) was unsuccessful. Likewise, use of the Gattermann-Koch reaction[153] did not lead to the desired product. Smith,[10] who experienced the same failure, termed this lack of discernible reaction "unexpected"

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[153] N. N. Crounse in R. Adams, op. cit., Vol. 5, pp. 290-300.

because of the ease with which toluene undergoes the same reaction.

Attention was turned to 2-cyanodibenzofuran as a possible chemical precursor of the aldehyde. Several workers[4] in this laboratory have prepared this nitrile, but no report of its preparation or properties has appeared in the chemical journals. A comprehensive study was made of the methods recommended[154] for the synthesis of aromatic nitriles. The Rosenmund-von Braun synthesis appeared to be the most attractive route. 2-Bromodibenzofuran was chosen as the starting halide because of its ease of preparation.

In this connection, it should be pointed out that direct bromination by bromine with[23] or without[96] ultraviolet irradiation appears to be the best procedure. The use of N-bromosuccinimide, which was suggested by French workers, has not proved advantageous;[23] the potent brominating agent, 1,3-dibromo-5,5-dimethylhydantoin, is claimed[155] to be without effect on dibenzofuran.

The reaction of 2-bromodibenzofuran with cuprous cyanide in quinoline solution at 180° gave uniformly good yields in the presence or absence of a nitrogen atmosphere in the reaction

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[154] D. T. Mowry, Chem. Revs., 42, 189 (1948).

[155] M. E. Fondovila, O. O. Orazi and J. F. Salellas, Anales asoc. quim. argentina, 39, 184 (1951) /C. A., 47, 2709 (1953)/.

flask. One run was made using 2-iododibenzofuran. There appears to be no advantage in the use of the iodo compound. However, in this case the use of a nitrogen atmosphere is indicated. At the reaction temperature of 180°, air oxidation of iodide ion to iodine apparently occurs. Iodination of the nitrile is conceivable if the reaction period is an extended one.

The variations in the yield of nitrile with changes in experimental procedure are not difficult to rationalize. It has been recorded[154] that differences in temperature and reaction time are reflected in the yield. A recent paper[156] reported that a variety of brominated polyclic hydrocarbons suffered dehalogenation on being heated at 280° in sealed tubes with cuprous cyanide, pyridine and water. The isolation of the nitrile when the water was omitted, and the formation of the amide at a temperature of 250° lend weight to the sequence of reactions which has been postulated:

$$ArBr \longrightarrow ArCN \longrightarrow Ar\overset{O}{\overset{\|}{C}}-NH_2 \longrightarrow ArCOOH \longrightarrow ArH$$

Thus, the low-melting samples of nitrile which were encountered in the course of this work may have been due to the presence of the parent heterocycle.

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[156] N. Campbell, J. E. McKail and J. Muir, Chemistry and Industry, 739 (1952).

The bromination of 3-nitrodibenzofuran according to the directions previously published[107] was accomplished in good yield. This compound could be the starting point in a series of steps leading to 3-nitro-8-dibenzofurancarboxaldehyde. It appears, however, the first intermediate, 2-cyano-7-nitrodibenzofuran, is much more susceptible to hydration and/or hydrolysis than the unsubstituted nitrile. Since the reduction of the cyano group without concomitant reduction of the nitro group poses difficulties, this approach was abandoned.

The 2-cyanodibenzofuran molecule suitably substituted with a group resistant to reduction represents another point of departure for a nuclearly-substituted 2-dibenzofurancarboxaldehyde.[157]

The bromination of 2-cyanodibenzofuran in glacial acetic acid did not yield the expected 2-bromo-8-cyanodibenzofuran, but a product which apparently is largely 2-bromo-8-dibenzofurancarboxamide. Though analytical data are not as accurate as might be desired, the amide grouping is indicated by the infrared spectrum and the lack of depression of melting point of an admixture with a sample of amide prepared from the acid obtained by hydrolysis of the amide. The substitution of

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[157]Because of the current commercial availability of 2-hydroxydibenzofuran (The Hilton-Davis Chemical Co., Cincinnati, Ohio), the synthesis of 2-hydroxy-3-dibenzofurancarboxaldehyde and perhaps 2-hydroxy-1-dibenzofurancarboxaldehyde by the Reimer-Tiemann reaction is an attractive possibility; however, only an ortho arrangement of substituents is possible.

bromine in the 8-position is indicated by the infrared spectrum of the amide and the acid. This assigned orientation is in agreement with that which has been demonstrated for the introduction of a substituent into a dibenzofuran molecule already bearing a deactivating group.[16]

The nitrile group of 2-cyanodibenzofuran was made the focal point of a number of reactions. Hydration gave 2-dibenzofurancarboxamide, a compound which was prepared but unreported previously. However, a better yield of amide was obtained by ammonolysis of the 2-dibenzofurancarboxylic acid chloride.

The reduction of 2-cyanodibenzofuran with 0.25 equivalent of lithium aluminum hydride was calculated to yield the heterocyclic aldehyde. From the reaction was isolated a gummy material which appeared to be unreacted nitrile. The great insolubility of the nitrile in ether forced the use of an ether-benzene mixture in which the nitrile was partly soluble.

The use of excess lithium aluminum hydride gave two substances which from examination of their spectra are concluded to be identical.

The spectra show absorption bands at 3.7μ and 3.9μ which are characteristic of primary amine hydrochlorides. The hydrochlorides as obtained from the reaction mixture possessed a fishy odor; they could not be recrystallized for analysis.

2-Cyanodibenzofuran also reacts with methanolic alkali to give the carboxylic acid, a compound required in large quantities in the writer's studies. It is perhaps most advantageous to hydrolyze the crude nitrile directly on obtaining it from the Rosenmund-von Braun reaction. This method cannot be recommended, however, as the most efficacious means for the preparation of the acid (though it is more convenient than operating via the Grignard reaction) because of the troublesome purification of 2-bromodibenzofuran.

One route to 2-dibenzofurancarboxaldehyde proceeds through the 2-chloromethyl compound. Kirkpatrick[7] has reported the successful chloromethylation of dibenzofuran. By means of the Sommelet reaction[158-161] then, it should be possible to obtain the desired aldehyde.

The absorption of hydrogen chloride by the acetic acid solution of dibenzofuran and zinc chloride indicated that the chloromethylation reaction was proceeding. However, complete polymerization[23] occurred during the attempted vacuum distillation of the product.

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[158] M. Sommelet, Compt. rend., 157, 852 (1913) /C. A., 8, 660 (1914)/.

[159] J. Graymore and D. R. Davies, J. Chem. Soc., 293 (1945).

[160] S. J. Angyal and R. C. Rassack, Nature, 161, 723 (1948).

[161] S. J. Angyal and R. C. Rassack, J. Chem. Soc., 2700 (1949).

Smith[10] attempted without success to carboxylate dibenzofuran directly by means of sealed tube reactions with carbon dioxide and a catalyst.

The use of oxalyl chloride[162] in a Friedel-Crafts reaction with anthracene[163,164] gives a fair yield of 9-anthroic acid.

This procedure was applied to dibenzofuran in an effort to obtain the 2-acid directly. The yield of 29.4% of acid offers some promise for the preparation of 2-dibenzofurancarboxylic acid in good yield directly from dibenzofuran. Proper modification of the reaction conditions (temperature, solvent, molar ratios) may enable one to obtain a higher yield than reported here.

The procedure which must be regarded at present as the method of choice for the preparation of the acid is the haloform reaction of 2-acetyldibenzofuran. The ketone is prepared readily, but it is separated from the unreacted dibenzofuran. This difficulty offers no problem, however, in the hypohalite oxidation. The alkali-insoluble dibenzofuran is simply removed by filtration at the conclusion of the reaction and relatively

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[162]For a survey of acid preparations by the use of oxalyl chloride see C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry", Reinhold Publishing Corp., New York, N. Y., 1941.

[163]H. G. Latham, Jr., E. L. May and E. Mosettig, J. Am. Chem. Soc., 70, 1079 (1948).

[164]E. A. Garlock, Jr. and E. Mosettig, ibid., 67, 2256 (1945).

pure 2-dibenzofurancarboxylic acid precipitates on acidification of the filtrate. If one desires to obtain the pure acetyl compound, careful vacuum distillation followed by chromatography would appear to be the most worthwhile method of purification. The use of benzene as a solvent for the reaction offers some advantage over the use of the usual Friedel-Crafts acylation solvents, nitrobenzene and tetrachloroethane. After completion of the hydrolysis, the benzene layer can be separated, washed, dried and then distilled, avoiding the lengthy steam distillation otherwise necessary. The ketone then can be distilled in the same apparatus. There is little formation of acetophenone in the acetylation of dibenzofuran by this procedure.

During one preparation of 2-dibenzofurancarboxylic acid by the hypochlorite oxidation of crude 2-acetyldibenzofuran, the writer failed to destroy with sodium bisulfite the excess hypochlorite at the conclusion of the reaction. Acidification of the reaction mixture then released chlorine as well as the free acid. The product obtained was one formed by the chlorination of 2-dibenzofurancarboxylic acid.

The chlorination of 2-dibenzofurancarboxylic acid would be expected to give 2-chloro-8-dibenzofurancarboxylic acid. The product formed in this case was not this acid in entirety, though its infrared spectrum was closely similar to that of 2-bromo-8-dibenzofurancarboxylic acid. The high chlorine

analysis and neutral equivalent indicate that the introduction of more than one halogen atom occurred to some extent.

The same mixture of chloro-acids was obtained on chlorination of 2-dibenzofurancarboxylic acid with acidified hypochlorite solution.

Decarboxylation of the chlorinated acid yielded a mixture which could not be resolved, and which apparently consisted of chloro- and dichlorodibenzofurans.

If this reaction could be regulated so as to give an isolable pure compound, it would prove to be a valuable route to the synthesis of halogenated acids in essentially a single step.[165]

The action of this chlorinating mixture on dibenzofuran itself yielded a mixture of broad melting range. This range narrowed but slightly on recrystallization, though the entire range was moved upward on the thermometric scale. This shifting was probably due to the concentrating of dichlorodibenzofuran. The spectrum of a fraction of this material (m.p. 146-149°) was congruent with that of Oatfield's[4] sample (m.p. 148°, soft 144°). Since the latter compound (or mixture) was prepared by the action of phosphorus pentachloride on potassium

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[165]The halogenating action of hypohalite in acid solution has been exploited frequently. The synthesis of 5-chloro-2-thiophenecarboxylic acid from 2-thiophenecarboxylic acid was executed in this manner. J. F. Bunnett, D. M. Bachman, L. P. Snipper and J. H. Maloney, J. Am. Chem. Soc., 71, 1493 (1949).

2-dibenzofuransulfonate, one of the chlorine atoms is indicated to be in the 2-position.

In recent years, the hydrazides of aromatic and heterocyclic acids have received attention as tuberculostatic agents.[166-169]

Only one hydrazide of the dibenzofuran series, viz., γ-(2-dibenzofuran)butyric acid hydrazide, has been previously reported.[24]

Since a number of esters of dibenzofurancarboxylic acids were available as the result of syntheses by the writer and Mr. K. Oita of this laboratory, the preparation of the corresponding hydrazides was undertaken.

2-Dibenzofurancarboxylic acid hydrazide, 4-dibenzofurancarboxylic acid hydrazide and 2-bromo-6-dibenzofurancarboxylic acid hydrazide were easily prepared in good yield from the methyl esters and hydrazine hydrate. The hydrazides were then converted to the benzenesulfonhydrazides by treatment with benzenesulfonyl chloride.

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

[167] J. Bernstein, W. P. Jambor, W. A. Lott, F. Pansy, B. A. Steinberg and H. L. Yale, ibid., 67, 366 (1953).

[168] H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry and J. Bernstein, J. Am. Chem. Soc., 75, 1933 (1953).

[169] Ng. Ph. Buu-Hoi, Ng. D. Xuong, F. Binon and Ng. H. Nam, Compt. rend., 235, 329 (1952) /C. A., 47, 2358 (1953)/.

It may be that combinations of the active hydrazide grouping and the dibenzofuran nucleus will show antituberculosis activity. It has been suggested[169] that the activity of the hydrazides against the tubercle bacillus is due to the formation of stable, poorly soluble copper complexes by the hydrazides. Thus the enzyme systems of the tubercule bacillus are disrupted. Buu-Hoi and co-workers claim that the free amino group of a hydrazide is not essential for activity; hence, the benzenesulfonhydrazides as well as the hydrazides were included among the compounds submitted to a government agency for physiological testing.

In the five years following the announcement[170] of the synthesis of chloramphenicol (Chloromycetin), many papers have appeared relative to the antibacterial activity of structural modifications of this antibiotic. However, relatively few reports have been concerned with the substitution of heterocyclic ring systems for the benzene ring in chloramphenicol.

The 5-nitro-2-furyl[171] (as the diacetate) and 5-nitro-2-thienyl[172,173] analogues of chloramphenicol have been prepared.

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[170] J. Controulis, M. C. Rebstock and H. M. Crooks, Jr., J. Am. Chem. Soc., 71, 2463 (1949).

[171] K. Hayes and G. Gever, J. Org. Chem., 16, 269 (1951).

[172] E. C. Hermann and A. Kreuchunas, J. Am. Chem. Soc., 74, 5168 (1952).

[173] C. F. Huebner, P. A. Diassi and C. R. Scholz, J. Org. Chem., 18, 21 (1953).

The 4-pyridyl analogue has also been reported.[174]

The preparation of a chloramphenicol type based on the dibenzofuran nucleus was undertaken in what apparently was the first attempt to substitute a polynuclear heterocycle for the benzene ring.

The synthetic method chosen was one based on the preparation of chloramphenicol through p-nitroacetophenone.[175]

2-Acetyldibenzofuran was brominated in the side chain as the first step. Though the preparation of 2-(ω-bromoacetyl)-dibenzofuran has been reported[7,30] no yield was given. In the writer's hands, the bromination of the ketone did not give entirely satisfactory results. The low yield may have been due to the presence of dibenzofuran in the ketone sample.

It seemed that a more satisfactory yield of bromoacetyl compound might be obtained by bromoacetylation of dibenzofuran.

When this reaction was carried out, the ketone produced melted over a wide range. Many recrystallizations were ineffective in narrowing the melting point range. Since aluminum chloride was used as the acylation catalyst, it is suggested that halogen interchange occurred between the catalyst and the methylene halogen of bromoacetyl bromide.

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[174] S. van der Meer, H. Kofman and H. Veldstra, Rec. trav. chim., 72, 236 (1953) [C. A., 48, 3361 (1954)].

[175] L. M. Long and H. D. Troutman, J. Am. Chem. Soc., 71, 2473 (1949).

Such an interchange between aluminum halide and the acyl halogen of an acid halide has been demonstrated.[176-178]

The analysis[179] of effluant gases obtained on hydrolysis of mixtures of aluminum halides and alkyl and arylalkyl halides support the contention that all four halogen atoms are equivalent in the intermediate ion $AlBrCl_3^-$ or $AlClBr_3^-$. On hydrolysis of the reaction mixture one would expect to obtain both ω-haloacetyldibenzofurans. The use of bromoacetyl bromide and aluminum chloride should give a 3:1 mixture with 2-(ω-chloroacetyl)dibenzofuran predominating.

Actually, the homogeneity of this phenacyl halide type was only of academic interest, since both compounds would react the same in the succeeding reaction. However, fairly pure bromoacetyl compound was obtained by chloride displacement with potassium bromide in acetone.

The use of aluminum bromide as catalyst would, of course, obviate these difficulties, but this material was not available at the time of these experiments.

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[176] F. Fairbrother, J. Chem. Soc., 503 (1937).

[177] J. F. Norris and J. E. Wood, J. Am. Chem. Soc., 62, 1428 (1940).

[178] G. Baddeley and D. Voss, J. Chem. Soc., 418 (1954).

[179] V. V. Korshak and G. S. Kolesnikov, J. Gen. Chem. (U. S. S. R.), 14, 1092 (1944) [C. A., 40, 4033 (1946)].

The formation of the hexamethylenetetramine salt of the crude 2-(ω-bromoacetyl)dibenzofuran and its decomposition in hydrochloric acid and ethanol gave 2-(ω-aminoacetyl)dibenzofuran hydrochloride. The amine hydrochloride was reacted in two portions with acetic anhydride and dichloroacetyl chloride to give respectively, 2-(ω-acetamidoacetyl)dibenzofuran and 2-(ω-dichloroacetamidoacetyl)dibenzofuran. The hydroxymethylation step was attempted with the former compound. The one trial was unsuccessful, a second could not be undertaken because of insufficient amounts of the acetamidoacetyl compound.

The procedures used in this step and those following were adapted from those of Long and Troutman[175] and Suter and coworkers.[180,181]

When the bromoacetylation of 3-nitrodibenzofuran was attempted, the use of aluminum chloride as catalyst again resulted in the formation of a mixture. This mixture was analyzed for bromine and nitrogen. The values obtained (Br, 15.09, 15.09; N, 4.82, 4.81) correspond closely to those calculated (Br, 15.17; N, 4.64) for a 3:1 mixture of 2-(ω-chloroacetyl)-7-nitrodibenzofuran and 2-(ω-bromoacetyl)-7-nitrodibenzofuran. The interchange mechanism is thus confirmed.

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[180] R. A. Cutler, R. J. Stenger and C. M. Suter, J. Am. Chem. Soc., 74, 5475 (1952).

[181] C. M. Suter, S. Schalit and R. A. Cutler, ibid., 75, 4330 (1953).

The failure to isolate a pure sample of 2-(ω-acetamidoacetyl)dibenzofuran is not readily explicable since a pure sample (based on total halogen content) of nitrohaloacetyldibenzofuran was used as a starting material. The high degree of insolubility of the ketone mixture in organic solvents in general probably is responsible, at least in part, for the poor results achieved.

It was during the investigation of Friedel-Crafts reactions with dibenzofuran that the writer noticed that two widely divergent melting points have been reported for 2-benzoyldibenzofuran. Borsche and Bothe[3] reported a melting point of 167-168° while Willis[17,182] claimed a value of 135-136° for the melting point of this compound. The melting points reported for the oximes also varied, being 234-235° and 182-183° respectively.

The writer repeated Willis' benzoylation of dibenzofuran and isolated two substances which according to their melting points corresponded to the "two" 2-benzoyldibenzofurans reported. It seemed probable that the higher melting of these two compounds was a dibenzoyldibenzofuran and the lower melting, a benzoyldibenzofuran. Though the calculated analytical values for the two ketones differ by less than 1% (for carbon), it was possible to differentiate between the two on this basis.

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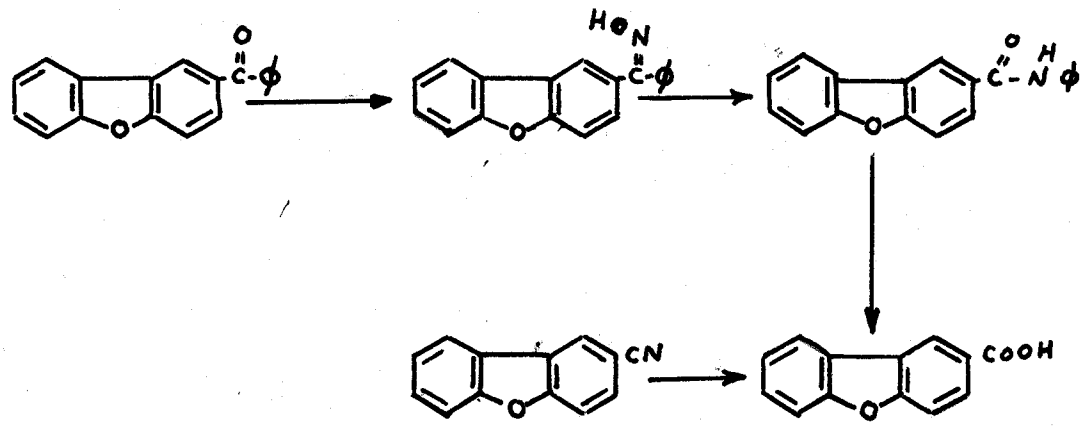
[182]H. B. Willis, Iowa St. Coll. J. Sci., 18, 98 (1943).

Analysis of the oximes confirmed the assignments made above.

The melting point of 231.5° found for dibenzoyldibenzofuran dioxime checks with the value of 234-235° reported for the supposed benzoyldibenzofuran. However, Willis' oxime of m.p. 182-183° was never isolated though the oximation reaction was run several times with a variety of modifications. It is suggested that his oxime is of configuration opposite to that isolated by the writer. The possibility remains, however, that the two oximes are different crystalline modifications of the same isomeric form. Unfortunately, the sample of Willis' oxime which was available was too small to permit Beckmann rearrangement for structure proof.

The writer's benzoyldibenzofuran oxime was rearranged to an amide which on hydrolysis yielded 2-dibenzofurancarboxylic acid. The structures of the compounds then must be as shown below.



The configuration of the oxime is assigned here in accordance with the generalization[183,184] that it is the trans group which migrates in the Beckman rearrangement of an oxime.

2-Benzoyldibenzofuran forms a hydrazone with difficulty; this is characteristic of diaryl ketones in general.[137] This compound never was isolated in pure form; there is only infrared spectrophotometric evidence for its formation. The hydrazone should rearrange[185] to an amide by trans migration. It would be of interest to determine if the anti-phenyl configuration is assumed in the hydrazone as in the oxime.

The 2,8-dibenzoyldibenzofuran structure has been assigned on the supposition that dibenzoylation occurs in the same manner as diacetylation.[125,186] Though the dioxime was formed in good yield, it could not be rearranged to the expected diamide, 2,8-dibenzofurandicarboxylic acid dianilide.

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[183] A. H. Blatt, Chem. Revs., 12, 215 (1933).

[184] B. Jones, ibid., 35, 335 (1944).

[185] D. E. Pearson, K. N. Carter and C. M. Greer, J. Am. Chem. Soc., 75, 5905 (1953).

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

Results of Phytohormonal Tests on Derivatives of Dibenzofuran and Other Compounds

A number of dibenzofuran derivatives and miscellaneous compounds described in the Experimental section were tested by the U. S. Army Chemical Corps at Camp Detrick, Maryland for plant hormone activity.

The results of the tests are summarized in Table 8. The low solubility of some of the dibenzofuran compounds in ethanol made it impossible to test these compounds in appreciable concentrations.

However,

> "the finding of one or a few inactive compounds, as e.g., certain of the acetic acid derivatives of pyridine, pyrrole, furan, thiazole, uracil, iminazole, carbazole and dibenzofuran, does not furnish an adequate basis for assuming that differently substituted derivatives of these nuclei also must be without activity."[187]

Ethyl 2-dibenzofuranoxyacetate[96] and 4-dibenzofuranoxyacetic acid[188] have also been synthesized and submitted for evaluation, but the results of the assays have not been received as yet.

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[187] A. G. Norman and R. L. Weintraub, First Symposium on Chemical-Biological Correlation, Chemical-Biological Coordination Center, National Research Council, National Academy of Science, Pub. No. 206, Washington, D. C., 1951, p. 48.

[188] K. Oita, unpublished studies.

Table 8

Phytohormonal Activities

Compound	Activity
2-bromo-8-dibenzofurancarboxamide (?)	-
dibenzofuran	-
2-dibenzofurancarboxamide	-
4-dibenzofurancarboxylic acid	-
2,8-dibenzofurandioxyacetic acid	-
2,8-dicyanodibenzofuran	-
3-nitrodibenzofuran	-
bis-1,2-(2,4-dichlorophenoxy)ethane	-
β-(2,4-dichlorophenoxy)ethyl chloride	-
β-(2,4-dichlorophenoxy)ethylmalonic acid	1/10 activity of 2,4-D
γ-(2,4-dichlorophenoxy)propyl chloride	-
δ-(2,4-dichlorophenoxy)valeric acid	-

SUMMARY

Tabulations have been made of the applications of dibenzofuran compounds to chemotherapeutic and other physiological uses.

A listing of dibenzofuran compounds reported since the issuance of the Chemical Abstracts Subject Index for 1951 has been presented.

A variety of experimental methods was unsuccessfully employed in efforts to synthesize 2-dibenzofurancarboxaldehyde.

The synthesis of 2-cyanodibenzofuran has been studied at some length and a number of derivatives and related dibenzofuran compounds was prepared.

Unsuccessful attempts were made to synthesize 2-chloromethyldibenzofuran.

2-Dibenzofurancarboxylic acid was synthesized by a number of procedures and several hydrazides were prepared from this and related acids.

A number of dibenzofuran analogues of chloramphenicol intermediates were prepared.

The compound identified in the literature as 2-benzoyldibenzofuran has been identified as a dibenzoyldibenzofuran; presumably 2,8-dibenzoyldibenzofuran.

The structure of the ketone of Willis has been confirmed to be 2-benzoyldibenzofuran.

A number of substituted aryl aliphatic ethers has been prepared in a search for plant hormones.

ACKNOWLEDGMENT

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