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Sulfur analogs of furan types

Arthur Lawrence Jacoby
Iowa State College

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SULFUR ANALOGS OF FURAN TYPES

BY

Arthur Lawrence Jacoby

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In charge of Major work

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Head of Major Department

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Dean of Graduate College

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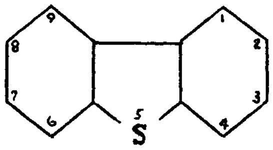
INTRODUCTION

Several years ago, in the course of the extensive study of furan in this laboratory, an investigation of dibenzofuran was undertaken with a view to eventually obtaining from it degradation products which would aid in the solution of the problem of orientation in furan. Furthermore, the fact that a reduced dibenzofuran nucleus forms a part of the morphine molecule stimulated the study of dibenzofuran chemistry in the hope that such work might assist in throwing light on the problem of morphine addiction. Coincidentally it was noted that the process of metalation[1] leads to derivatives of certain aromatic nuclei with substituents in positions not ordinarily affected by the commoner substitution processes such as halogenation, nitration, sulfonation, and the Friedel-Crafts reaction. A natural step further, then, was to an investigation of dibenzothiophene, the sulfur analog of dibenzofuran.



Dibenzothiophene

The study of this sulfur compound is of immediate interest for two other reasons: the replacement of oxygen by sulfur in certain organic compounds (e.g., the barbiturates[2]) has been observed to produce desirable character-

(1) Metalation is the term applied to the replacement of hydrogen attached to carbon by a metal to give a true organometallic linkage. Gilman and Young, J. Am. Chem. Soc., 56, 1415 (1934).
(2) Tabern and Volwiler, J. Am. Chem. Soc., 57, 1961 (1935).

istics in their physiological action; and the sulfur atom, on account of the possibility of oxidation to sulfoxides and sulfones, presents the opportunity to greatly increase the number of interesting compounds for test purposes.

The great differences in relative reactivity of organometallic compounds, which, in a certain sense, are practically equivalent to differences in kind of reaction as well as rate of reaction, have warranted the prediction[3] that selective, preferential reactions of organometallic compounds might be found by exercising the proper choice. Substantiation of this prediction came when it was shown[4] that, while dibenzofuran is metalated in the 4-position by organoalkali compounds, phenylcalcium iodide, and mercuric acetate, the analogous heterocycle carbazole is metalated in the 4-position by organoalkali compounds and in the 2-position by mercuric acetate. This remarkable behavior, resulting from the mere change from oxygen as the hetero atom to nitrogen, lent impetus to the investigation of the effect of various organometallic compounds on dibenzothiophene.

Many of the dibenzothiophene derivatives prepared were tested for toxicity and their ability to produce hypnosis in the white mouse by Dr. W. G. Bywater of Parke, Davis and Company. Dr. Oliver Kamm of the same company kindly tested several of the compounds for their activity against streptococcic infections. Several compounds were synthesized in consideration of the possibility of their possessing estrogenic activity, and thanks are due to Dr. Edward A. Doisy, of the University of St. Louis, who conducted the biological assays. Toward the close of this research several compounds

(3) Gilman and Nelson, Rec. trav. chim., 55, 526 (1936).
(4) Gilman and Kirby, J. Org. Chem., I, 146 (1936).

were sent to Dr. Isabella Perry of the University of California to be tested for possible carcinogenic activity.

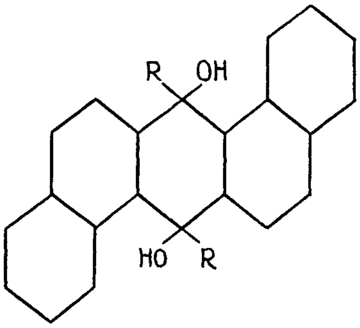
Even before the structure of the estrogenic hormones had been completely elucidated, Cook and co-workers[5] set about to examine certain synthetic compounds for their ability to produce the estrous response. Since evidence then in hand indicated that the estrogenic hormones were hydrogenated phenanthrenes containing oxygen, a number of compounds bearing a superficial resemblance in one or both of these respects were submitted to tests. It soon became apparent that estrogenic activity is not specific in any degree and that compounds ranging from completely aromatic hydrocarbons to partially hydrogenated hydrocarbons and the diols prepared from various anthracenes are all represented among the estrogenic types. Totally unrelated to the natural hormones, 1,9-dimethylphenanthrene, 9-ethylphenanthrene[6], and the carcinogenic hydrocarbons 3,4-benzpyrene and 5,6-cyclopenteno-1,2-benzanthracene were found to be active in producing estrus. Many oxygenated compounds containing the phenanthrene ring system were found to be active. Important representatives of this type include 1-keto-1,2,3,4-tetrahydrophenanthrene, 6-hydroxy- and 6,7-dihydroxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-11,12-dicarboxylic acid anhydrides and the corresponding methyl ethers, and 2-phenanthreneacetic acid.[6]

Two years later, Dodds and Lawson[7] reported the activity of a wide variety of compounds which did not contain the phenanthrene ring system. The list included 1,2-dihydroxy-1,2-di-α-naphthylacenaphthene; 1,1-di-α-

(5) Cook, Dodds, Hewett, and Lawson, *Proc. Roy. Soc.* (London), **114 B**, 272-286 (1934).
(6) Reported by Thayer, MacCorquodale, and Doisy, *J. Pharm. Exp. Ther.*, **59**, 48-53 (1937).
(7) Dodds and Lawson, *Nature*, **137**, 996 (1936).

naphthylacenaphthene; diphenyl-α-naphthylcarbinol; di-(p-hydroxyphenyl)-dimethylmethane, di-(4-hydroxy-3-methylphenyl)-1,1-cyclohexane, 4,4'-dihydroxybenzophenone, and 4,4'-dihydroxybiphenyl.

In their first report[5], Cook and co-workers reported the activity of several diols related to the carcinogenic hydrocarbon 1,2,5,6-dibenzanthracene.



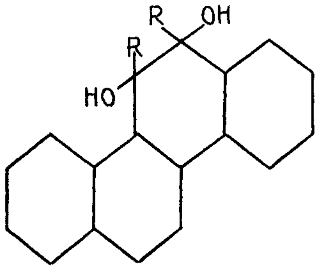
9,10-Dialkyl-9,10-dihydroxy-9,10-dihydro-
1,2,5,6-dibenzanthracene

An interesting relation was found to exist between the activity and molecular weight where the alkyl groups were normal hydrocarbon chains. While the methyl derivative was inactive, the n-propyl derivative was the most potent, comparing favorably with estriol, and the activity dropped markedly in the n-butyl derivative and disappeared completely in the n-amyl compound.

Following the lead established in their earlier work, Cook and co-workers[8] prepared several other alkyl derivatives and the phenyl derivative of the above. Activity was noted where the R groups were cyclopentyl and phenyl. They then extended their investigation to include derivatives of 1,2-dihydroxy-1,2-dihydrochrysene (I), 9,10-dihydroxy-9,10-dihydrophenanthrene

(8) Cook, Dodds, and Lawson, Proc. Roy. Soc. (London), 121 B, 133-141 (1936).

(II), 9,10-dihydroxy-9,10-dihydro-1,2-benzanthracene (III), and 9,10-dihydroxy-9,10-dihydro-2,3-benzanthracene (IV).



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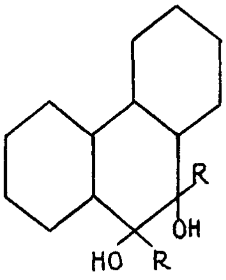

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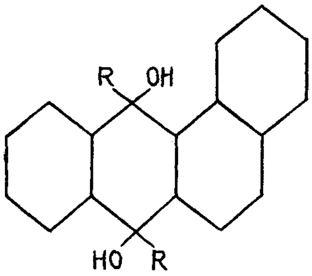
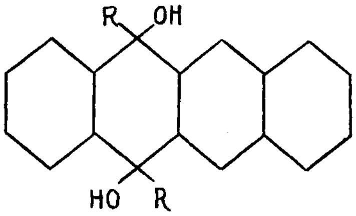


III



IV

Activity of a low order was noted in 1,2-diphenyl-1,2-dihydrochrysene (I, R = phenyl) and 9,10-diphenyl-9,10-dihydro-1,2-benzanthracene (III, R = phenyl). A few months prior to the second report[8] of Cook, Bachmann and Bradbury[9] synthesized and reported the activity of the 9,10-diethyl, the 5-phenyl-9,10-diethyl, and the 5-phenyl-9,10-di-n-propyl derivatives of 9,10-dihydroxy-9,10-dihydro-1,2-benzanthracene (III).

The most common method[10, 11] of testing synthetic compounds for estro-

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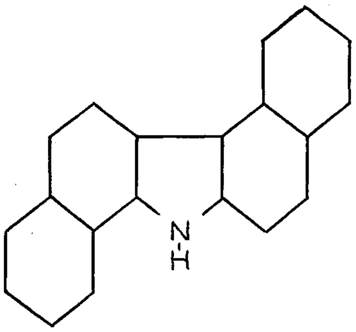
(9) Bachmann and Bradbury, J. Org. Chem., 2, 175-182 (1937).
(10) Munch, "Bioassays", Williams and Wilkins Co., Baltimore (1931), pp. 654-658; Burn, "Methods of Biological Assay", Milforn, New York (1928), pp. 96-103.
(11) Private communication to Dr. Henry Gilman from Dr. E. A. Doisy.

genic activity consists of injecting the material, either subcutaneously or intraperitoneally, in oil or in water, into ovariectomized mice or rats. After removal of the ovaries from medium-sized female mice, vaginal smears are made for two to three weeks to be sure of the completeness of the removal. The animals are then primed with a quantity of some standard estrogenic material (e.g., theelin) sufficient to produce estrus in the average ovariectomized mouse. A week later slightly less than this dose is administered and those showing negative tests are discarded as lacking in susceptibility. A week later a third injection is made, this time using slightly less than the average minimum effective dose. Mice showing a positive test under these conditions are discarded as being hypersusceptible. The remaining mice are then considered suitable for test purposes.

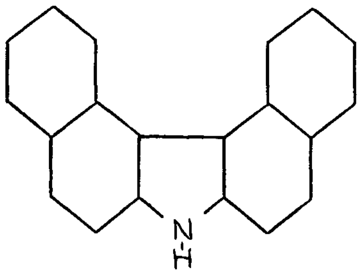
As a preliminary survey in the testing of new material, two to five mice are injected with 25 mg. of the compound. If the compounds are not active in that dosage it is felt that further assay is not justified. However, if the compounds are found active, the complete assay requires the injection of from 25 to 50 animals. In the preliminary survey, the 25 mg. of material is injected in three equal quantities on successive days, the total solvent being one cubic centimeter of oil or water where the solubility permits. The contents of the vagina are then examined under the microscope 32 hours after the last injection and then on each morning and evening for three days. The state of estrus is identified by the skilled observer by the types and relative amounts of the various cells taken in the smear.

The possibility of derivatives of dibenzothiophene possessing carcinogenic activity has also been considered, incidental to this research, and several compounds have been sent to Dr. Isabella Perry of the University of California, who kindly consented to conduct the physiological tests. It is appropriate to state at this point that some of the earlier work[12] from this laboratory has dealt with a consideration of compounds, particularly of the organolead type, which might be useful in the treatment and cure of cancer.

It is unlikely that dibenzothiophene itself would be found to be a carcinogen since dibenzofuran is inactive and, in general, more complexity of structure exists in those compounds which have been found to be carcinogenic. However, polynuclear compounds containing the dibenzothiophene nucleus are of interest since both 1,2,6,7- and 1,2,8,9-dibenzcarbazole have been shown to be active[13].



1,2,6,7-Dibenzcarbazole



1,2,8,9-Dibenzcarbazole

3,4,6,7-Dibenzcarbazole is less active, and the simpler compound, 3,4-benzcarbazole, produces epithelial growths which, however, have not definitely been identified as epitheliomas or cancer of the skin. Other synthetic carcinogenic agents containing nitrogen in their ring system include

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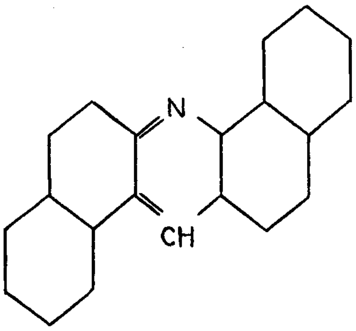
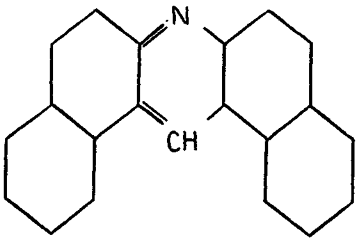
(12) Towne, Doctoral Thesis, Iowa State College (1932), pp. 56-58; Robinson, Doctoral Thesis, Iowa State College (1929), pp. 6-18.

(13) Cook and co-workers, Am. J. Cancer, 29, 224 (1937).

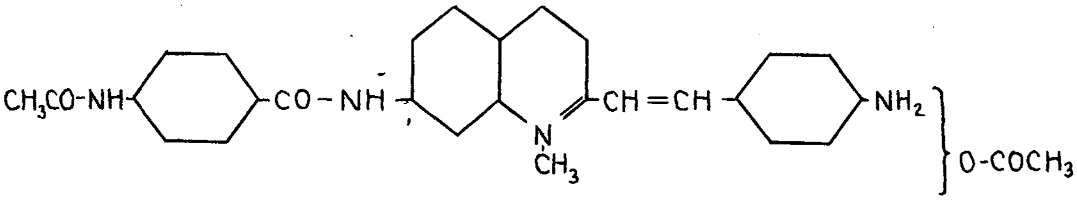
1,2,5,6- and 3,4,5,6-dibenzacridine[14] and 2-(p-aminostyryl)-6-(p-acetaminobenzamino)-1-methylquinolinium acetate (V)[15].



1,2,5,6-Dibenzacridine



3,4,5,6-Dibenzacridine



V

The search for synthetic carcinogenic compounds was initiated in 1915 when Yamagiwa and Ichikawa[16], studying the high incidence of cancer among chimney sweeps and workers with coal tar, discovered that the repeated application of coal tar to the ear skin of the rabbit produced skin cancer. Nine years earlier, in Germany, B. Fischer[17] had noted the cell prolifer-

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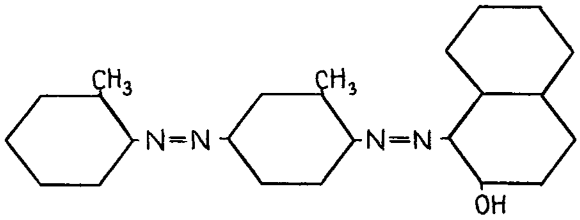
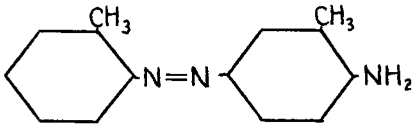
(14) Barry and co-workers, Proc. Roy. Soc. (London), 117 B, 318-351 (1935).
(15) Browning, Gulbransen, and Niven, J. Path. Bact., 42, 155-159 (1936).
(16) Yamagiwa and Ichikawa, Mitteil. med. Fakultät., kaiser. Univ. Tokyo, 15, 295 (1915)[Cook, Chem. Week., 32, 563-66 (1935)].
(17) Fischer, München. med. Wchnschr., 53, 2041-47 (1906)[Shear, Am. J. Cancer, 29, 269 (1937)].

ation caused by injecting a solution of the dye scarlet red into the ear of a rabbit. At that time he suggested the connection between his experiment and the production of cancer but, since the cell proliferation noted was not thought to be malignant, scarlet red, and later the active part of the molecule, 2-amino-5-azotoluene, were used in salves to promote the healing of wounds. It was not until 1932 that Yoshida[18] demonstrated the fact that 2-amino-5-azotoluene is definitely carcinogenic to experimental animals.



Scarlet red



2-Amino-5-azotoluene

Following the discovery of the carcinogenic action of coal tar, there was begun an extensive investigation of numerous aromatic hydrocarbons[19], notably by Kennaway and Cook at the Research Institute of the Cancer Hospital, London, and by Fieser and Shear of Harvard University and the U. S. Public Health Service, working on the idea that any increase in our knowledge of the cause of cancer would prove of value in studying the cure. To Cook and Kennaway and their co-workers belongs the distinction of dis-

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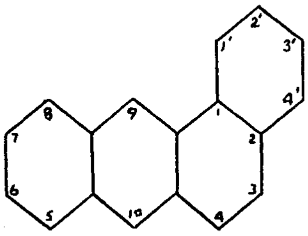
(18) Sasaki and Yoshida, *Arch. path. anat.* (Virchow's), *295*, 175-200 /*C.A.*, *30*, 7195 (1936)/; Miuda, *Bull. assoc. franç. étude cancer*, *24*, 534-38 (1935)/*C.A.*, *30*, 5290 (1936)/.

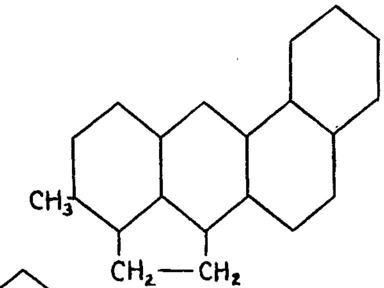
(19) The reader is referred to the following reviews covering the work on the hydrocarbons. Cook, *Chem. Week.*, *32*, 563-66 (1935); Cook and co-workers, *Am. J. Cancer*, *29*, 219-59 (1937); Fieser, "Chemistry of Natural Products Related to Phenanthrene", Reinhold Pub. Corp., New York (1936), pp. 81-110.

covering the first synthetic hydrocarbon of known structure to produce cancer. Earlier observations that the mixtures of hydrocarbons obtained either by heating isoprene and acetylene to high temperatures in the presence of hydrogen or by treating tetrahydronaphthalene with aluminum chloride were carcinogenic convinced these investigators that the active agent of coal tar was probably a hydrocarbon. Further work resulted in the discovery of the carcinogenic compound, 1,2,5,6-dibenzanthracene. Subsequent developments showed that various derivatives of 1,2-benzanthracene are carcinogenic, and, indeed, the most potent carcinogens known today fall into this category.

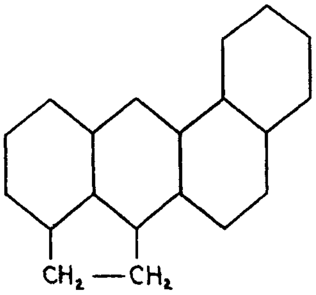
Although 1,2-benzanthracene (VI) itself is practically without activity, many of its derivatives were studied and it became apparent that substituents in the 5- or 6-positions were especially effective in producing carcinogenicity. Methylcholanthrene (VII), and cholanthrene (VIII) are two of the most potent carcinogens known and each is a derivative of 1,2-benzanthracene with substituents in the 5- (and 10-) position.



VI

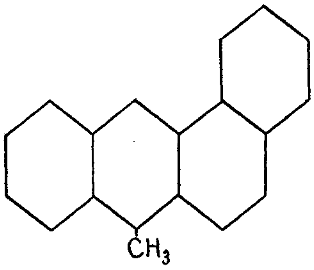


VII

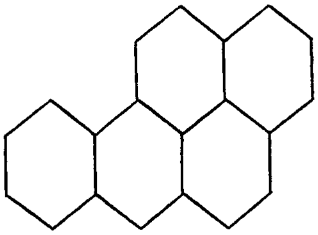


VIII

Substitution in both meso positions of 1,2-benzanthracene led to complete absence of activity and caused Cook to conclude that the meso hydrogens played some part in the production of cancer. Later work by Fieser, Shear, and co-workers on the effect of modifications of the cholanthrene molecule showed that substitution in *one* of the meso positions contributed to the potency of 1,2-benzanthracene, since 10-methyl-1,2-benzanthracene is practically as active as cholanthrene itself. Therefore, cholanthrene owes its activity not to the five-membered ring as originally supposed by Cook but merely to the fact that it contains a carbon substituent in the meso position 10. 3,4-Benzpyrene, the only carcinogenic hydrocarbon to be isolated from coal tar and identified, may be regarded as a derivative of 1,2-benzanthracene with a substituent in the meso position 9. The activity of 3,4-benzpyrene is comparable to that of cholanthrene.



10-Methyl-1,2-benzanthracene



3,4-Benzpyrene

Evidence appearing up to 1936 indicated that for a hydrocarbon to be carcinogenic it must contain a condensed ring system of four or five rings or the phenanthrene nucleus (e.g., 3,4-benzphenanthrene). However, in 1936, Morton, Branch, and Clapp[20] announced the discovery that *sym*-triphenylbenzene and tetraphenylmethane are carcinogenic. The former was tested both by injection and painting; the latter was tested only by painting.

(20) Morton, Branch, and Clapp, *Am. J. Cancer*, *26*, 754 (1936).

Both compounds were inferior in potency to 1,2,5,6-dibenzanthracene. Later work by Shear has cast some doubt on the carcinogenicity of triphenylbenzene since a specially purified sample injected subcutaneously gave no tumors in 13 months. Today, with an increasing knowledge of synthetic organic compounds capable of inducing malignancy, it can only be said that the feature common to all is the presence of at least two benzene rings.

The production of water-soluble carcinogenic agents for injection has been eagerly sought after by many investigators. The first to be found was the sodium salt of 1,2,5,6-dibenzanthracene-9,10-endo-α,β-succinic acid[13], formed by the condensation of maleic anhydride with the dibenzanthracene. The styryl compound which was mentioned above is also injected in water solution, being soluble to the extent of two per cent. The most recent trend in this study has been the synthesis of various hydroxy derivatives. 3-Hydroxy-1,2-benzanthracene and its methyl ether were found to be active although somewhat irregular in their action. 4'-Hydroxy-3,4-benzpyrene, having its hydroxyl group in the position corresponding to position 5 of the 1,2-benzanthracene system, is inactive.

In the earliest work with the hydrocarbons, testing was accomplished by painting the skin of the test animal with a benzene solution of the compound being tested, the concentration of the solution being usually about 0.3 per cent and the applications being repeated frequently for a certain period of time. Later methods which have been developed include the subcutaneous injection of the compound in lard or some oil. One of the easiest and most reliable methods in use at present consists of the subcutaneous injection of the crystalline compound, lubricated with a small amount of glycerol. The application to the skin generally results in epitheliomas or skin cancers, while the injections lead to the formation of sarcomas or cancer of the connective tissues, and often metastases are observed, wherein the malignant cells have migrated to another portion of the body and there set up new tumors. One of the most decisive tests for the malignancy of a tumorous growth is the successful transplanting of the cancerous growth to a site in another animal.

In the work with the high-molecular weight hydrocarbons it has been shown that a quantity of 1,2,5,6-dibenzanthracene as small as 4 γ, injected subcutaneously in a pellet of cholesterol, was capable of producing a sarcoma[21]. Therefore, the idea arises that some minute trace of impurity common to all the high-molecular weight hydrocarbons which were found to be carcinogenic is responsible for their activity. However, this theory is weakened by the discovery of the carcinogenicity of the styryl compound and the aminoazotoluene, since the methods of synthesis of these latter may be supposed to exclude the presence of compounds which might accompany the hydrocarbons.

As was suggested before, the possibility of oxidation of the nuclear sulfur of dibenzothiophene opens a wide field of investigation unattainable with the analogous dibenzofurans and carbazoles. Since some of the most interesting sulfoxides and sulfones now being studied are those which are found to possess strong antistreptococcic activity, attention has also been directed toward such possibilities in this research. A brief view of some of the latest discoveries in this field will make readily apparent the

(21) Shear, Am. J. Cancer, 26, 322 (1936).

similarity between already known agents and the possible dibenzothiophene oxidation products.

Sulfanilamide (p-aminobenzenesulfonamide) was at first considered to be the most important agent in the cure of streptococcic infections and the theory has been advanced that other active agents owe their antistreptococcic activity to the fact that they undergo conversion in the body to sulfanilamide[22]. Recent developments of more immediate interest to this research cast doubt upon the validity of this theory as to the mode of action. Buttle and co-workers[23] have lately demonstrated the high degree of potency of 4,4'-dinitro- and 4,4'-diaminodiphenyl sulfone. The former was less toxic and equally as active in mice as sulfanilamide. The diamino compound was found to be 100 times as active as sulfanilamide and 25 times as toxic, giving it an effectiveness of about four times that of the older agent. The corresponding sulfoxides have been studied by Andre and Guy and co-workers[24]. These investigators found maximum activity in the compounds studied to be in 4-nitro-4'-aminodiphenyl sulfoxide and the corresponding sulfone. In either case this activity was reported as being about 100 times that of sulfanilamide.

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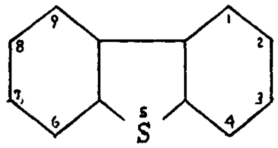
(22) Trefouel, Trefouel, Nitti, and Bovet, Presse. med., 45, 839 (1937) /C. A. 31, 8695 (1937)/

(23) Buttle and co-workers, Lancet, 1937 (I), 1331.

(24) Andre, Andre, and Guy, Nature, 140, 283 (1937); Levadite, Andre, Vaisman, Andre, and Guy, Compt. rend., 205, 1018 (1937).

DISCUSSION

Occurrence and preparation. Dibenzothiophene, frequently referred to as diphenylene sulfide, was first isolated by Stenhouse[25] who prepared it by passing the vapor of diphenyl sulfide through a hot iron tube filled with nails. The product crystallized from alcohol in small white needles and melted at 94°. However, he incorrectly analyzed the substance and regarded it as an isomer of the starting material and called it "para phenyl sulfide". The sulfone which he obtained by heating his product with potassium dichromate and dilute sulfuric acid melted at 230° and also gave him analyses which led him to believe it was of the formula $C_{12}H_{10}SO_2$. The correct structural formula of dibenzothiophene appears below, together with the numbering system approved by the International Rules for the Numbering of Organic Ring Systems.



This numbering system is used throughout this thesis, although the literature of French, English, and German workers most frequently employs the older system.

Four years after the work of Stenhouse, Graebe[26], while studying the behavior of various biphenyl compounds and the synthesis of phenanthrene and carbazole, repeated the experiment of Stenhouse and showed that the product actually had the formula $C_{12}H_8S$ and, in the light of his other work,

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(25) Stenhouse, Ann., 156, 332 (1870).
(26) Graebe, Ber., 7, 50 (1874); Ann., 174, 185-89 (1874).

was undoubtedly dibenzothiophene. Graebe's product melted at 97°, boiled unchanged at normal pressures at 332-333°, and gave the sulfone of melting point 230° which was also analyzed correctly.

Dibenzothiophene occurs naturally in the liquid coal tar fractions, as was shown by Kraemer and Weissgerber[27], and Kruber[28], and can be removed from crude phenanthrene, in which it appears as a contaminant, by treating an acetic acid solution of the phenanthrene with hydrogen peroxide, causing the difficultly soluble sulfone to precipitate.

The first preparative method for the production of dibenzothiophene to appear in the literature was that described in a patent[29]. By this method, 2,2'-dihydroxybiphenyl, obtained by alkali fusion of dibenzofuran, is heated to a high temperature with phosphorus pentasulfide. The resulting dibenzothiophene is distilled from the mixture in "commercially satisfactory" yields and, after recrystallization from glacial acetic acid or dilute alcohol, melts at 98.5°.

Following this, in 1932 there appeared a method by Schoenberg[30] in which he treated diphenyl sulfoxide in boiling toluene solution with powdered sodamide. The melting point which he reported was 97-8°, and the yields by this process were poor, ranging about 25 per cent. Later, Courtot, Chaix, and Nicolas[31] reported an improvement in this process by replacing the toluene with benzene, thus obtaining a 32 per cent yield of dibenzothiophene.

(27) Kraemer and Weissgerber, Ber., 34, 1665 (1901).
(28) Kruber, Ber., 53, 1566 (1920).
(29) Lange, Widmann, and Wennerberg, D. R. P. 330, 833 /Chem. Zentr., 1921 II, 265/.
(30) Schoenberg, Ber., 56B, 2275 (1923).
(31) Courtot, Chaix, and Nicolas, Compt. rend., 194, 1660 (1932).

The best method known today for the synthesis, and the one used with slight revision, throughout this investigation, is the one described in a German patent of 1933[32]. By this method as high as an 80 per cent yield of the product has been reported by heating together the theoretical quantities of biphenyl and sulfur, with a small amount of anhydrous aluminum chloride to act as a catalyst. During the heating, which eventually reaches 240°, hydrogen sulfide is evolved and when the cooled mass is extracted with water, followed by alcohol, the alcohol extracts yield a crude product of a light tan color which is entirely satisfactory for many synthetic purposes without any further treatment. Since many of the syntheses dealt with in this work involved the treatment of the dibenzothiophene with an organometallic compound, it was necessary to purify it beyond the state which is attained by recrystallizations alone. Distillation under diminished pressure, followed by a single recrystallization from alcohol, gives beautiful, long, colorless needles, m.p. 99°. This material gives maximum yields of metalation products when treated with organometallic compounds, and is pure enough so that a sample kept in the laboratory was repeatedly used, with excellent results, to check the apparatus and reagents used in the determination of carbon, hydrogen, and sulfur.

One other method for the preparation of dibenzothiophene which is of interest more from a theoretical standpoint rather than as a method of synthesis is the reaction of sulfur with dibenzothiophene-5-dioxide, developed independently in the course of this work and by Cullinane and Davies[33] in 1936. A relatively rich source of dibenzothiophene-5-dioxide, and the

(32) Tschunkur and Himmer, D. R. P. 579, 917 (1933) /C. A., 28, 1053 (1934)/.
(33) Cullinane and Davies, Rec. trav. chim., 55, 881-86 (1936).

one drawn upon by Cullinane, is the tetrazotization and removal of the amine groups of benzidine sulfone, a readily available material. It will be seen that this reaction is an unusual one, namely, the conversion of a sulfone to the corresponding sulfide. The possible ramifications of the reaction will be discussed further on.

Substitution in dibenzothiophene. It was not until 1926 that any extensive study of the chemistry of dibenzothiophene was undertaken. In that year Courtot published the first of his series of articles relating to orientation in the heterocycle and since has done much to clarify the problem. It has been shown by Courtot and his co-workers that nitration[34], halogenation[35], and sulfonation[36] involve the same position in the nucleus. By carefully regulating the conditions of the reaction, Courtot and Pomonis[34] found that dibenzothiophene could be mononitrated in 40 per cent yield. Reduction of the nitro derivative with zinc in boiling alcoholic ammonia gave the corresponding amine. Further nitration of the mononitro derivative gave a dinitrodibenzothiophene. This could be reduced to the corresponding diamino derivative by the use of tin and hydrochloric acid.

Bromination[35] of dibenzothiophene was found to give either a mono- or a dibromo derivative, depending upon the amount of bromine employed. These bromo compounds were then shown to be identical with the bromo compounds obtained from the products of mono- and dinitration of dibenzothiophene, by reduction, diazotization, and replacement of the amino groups by bromine. Furthermore, the same bromo-nitrodibenzothiophene was obtained by the

(34) Courtot and Pomonis, Compt. rend., 182, 931 (1926).
(35) Courtot, Nicolas, and Liang, ibid., 186, 1624 (1928).
(36) Courtot and Kelner, ibid., 198, 2003 (1934).

bromination of nitrodibenzothiophene or the nitration of bromodibenzothiophene.

In order to show that sulfonation involves the same position in the nucleus as nitration, the sulfonic acid obtained by the treatment of dibenzothiophene with chlorosulfonic acid was converted through the sulfinic acid to the corresponding thiol. This, then, was shown to be identical with the thiol obtained from nitrodibenzothiophene by reduction of the nitro group, diazotization, treatment with ethyl xanthate, and hydrolysis of the resulting ester with potassium hydroxide. Nitration of dibenzothiophenesulfonic acid or sulfonation of nitrodibenzothiophene led to the same nitrodibenzothiophenesulfonic acid in each case.

Having shown that nitration and halogenation involve the same positions in the nucleus and that disubstitution occurs to give products in which the substituents occupy positions symmetrical to each other with respect to the sulfur atom, Courtot[37] then showed that monosubstitution of dibenzothiophene occurs either ortho or para to the sulfur linkage. Alkaline fusion of dibenzothiophene-5-dioxide normally leads to the formation of 2-hydroxybiphenyl. By careful handling of this reaction, it was shown that it was possible to stop it at an intermediate stage and isolate biphenyl-2-sulfonic acid. By applying this procedure to the sulfone formed by the oxidation of the dibromodibenzothiophene described above, a new dibromobiphenyl-2-sulfonic acid was obtained. This acid, when treated in a sealed tube with concentrated hydrobromic acid, gave 3,3'-dibromobiphenyl. Thus it was demonstrated that the bromine atoms in the original dibenzothiophene derivative were in

(37) Courtot and Chaix, Compt. rend., 192, 1667 (1931).

positons meta to the biphenyl bridge.

In order to decide between positions 2 or 4 as the one involved in monosubstitution, Courtot[38] diazotized the amine group of 2-amino-5-bromobiphenyl and replaced it by the sulfinic acid group. This was then oxidized to the corresponding sulfonic acid, converted to the acid chloride, and treated in nitrobenzene solution with anhydrous aluminum chloride. This procedure resulted in an intramolecular condensation of the Friedel-Crafts type to give authentic 2-bromodibenzothiophene-5-dioxide. When this compound was shown to be identical with the sulfone of the product of monobromination of dibenzothiophene it was definitely established that the substitution processes thus far dealt with affect the 2- and 2,8-positions of the nucleus.

The constitution of 2-nitrodibenzothiophene was confirmed in 1936 by Cullinane, Davies, and Davies[39]. Starting with 2,4-dinitrodiphenyl sulfide, these investigators reduced the 2-nitro group, diazotized the resulting amine, and closed the ring between the 2- and 2'-positions to give 2-nitrodibenzothiophene.

This reaction is similar to a preparation of dibenzothiophene reported by Schwechten[40], who tetrazotized 2,2'-diaminodiphenyl sulfide and thus formed the biphenyl linkage to give dibenzothiophene.

In studying further the orientation in the dibenzothiophene nucleus, acetylation by the Friedel-Crafts method was investigated. When dibenzothiophene in carbon disulfide solution is treated with the calculated amount of acetyl chloride, in the presence of anhydrous aluminum chloride, a 70

(38) Courtot, Compt. rend., 198, 2260 (1934).
(39) Cullinane, Davies, and Davies, J. Chem. Soc., 1435-37 (1936).
(40) Schwechten, Ber., 65, 1608 (1932).

per cent yield of a monoacetyldibenzothiophene is obtained. The structure of this material was established as being 2-acetyldibenzothiophene by oxidation with iodine and sodium hydroxide after the method of Fuson and Tullock[41]. It was thus converted to a dibenzothiophenecarboxylic acid which was identified with the acid first prepared by Courtot[35] from 2-bromodibenzothiophene by treatment with magnesium followed by carbon dioxide. A mixed melting point of the corresponding methyl esters showed no depression.

Dibenzothiophene was found to undergo metalation when treated with various organolithium compounds in ether solution. Carbonation of the reaction mixture from the metalation with *n*-butyllithium gives a high yield of a monobasic acid of dibenzothiophene. When this acid and its methyl ester were both found to be unlike the corresponding 2-derivatives, steps were taken to determine whether metalation might not have involved the 4-position, as is the case in the related nuclei dibenzofuran and carbazole. Dibenzothienyllithium, prepared as in the synthesis of the carboxylic acid, was treated with methyl sulfate. The resulting methyldibenzothiophene was separated from its homolog by reason of its greater solubility in alcohol, from which the starting material may be made to separate while the desired product is retained in solution. This methyldibenzothiophene was then compared with authentic 4-methyldibenzothiophene and found identical by the method of mixed melting points. The authentic material was prepared by ring closure, starting with 3-methyl-2,2'-dihydroxybiphenyl and heating with phosphorus pentasulfide until the cyclic product distilled.

(41) Fuson and Tullock, *J. Am. Chem. Soc.*, *56*, 1638 (1934).

Not only was the dibenzothiophene-4-carboxylic acid obtainable by metalation with n-butyllithium, but other organolithium compounds were also found to metalate the nucleus in the 4-position. The yields of acid obtained from n-butyl-,* phenyl-, α-naphthyl-, and p-anisyllithium were found to be approximately 55, 12, 7.6 and 0 per cent, respectively. In the case of p-anisyllithium, an anomolous behavior of the metalating agent was noted which might be assumed to have some influence on the failure to obtain any metalation of dibenzothiophene. It was found that, while the reaction of p-bromoanisole and lithium in ether medium proceeds smoothly to give p-anisyllithium, as evidenced by the production of p-anisic acid and 4,4'-dimethoxybenzophenone on carbonation of the reaction mixture, prolonged heating of the ether solution of the organometallic compound, followed by carbonation, leads to an unknown acid, melting at 120-21°, which has not yet been identified. However, even if the p-anisyllithium were not thus altered during the reaction, the yield of acid by this metalation would be predicted to be very low on account of the position of the p-anisyl radical in the electronegativity series of Kharasch[42].

Phenylcalcium iodide metalates dibenzofuran in the same position as do the organolithium compounds. However, treatment of dibenzothiophene with phenylcalcium iodide followed by carbonation gives a third monobasic dibenzothiophene acid, different from the 2- and 4-acids. It is found to melt or decompose at about 300-305°, and its methyl ester also melts considerably higher than the corresponding 2- and 4-esters. By a comparison with the

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* Mr. H. A. Pacevitz has obtained as high as 65% yield of the crude dibenzothiophene-4-carboxylic acid by metalation with n-butyllithium.

(42) Kharasch and Flenner, J. Am. Chem. Soc., 54, 674 (1932).

melting points of the known dibenzofurancarboxylic acids, the high melting point of this new acid would indicate that it is probably dibenzothiophene-3-carboxylic acid. Decarboxylation gives dibenzothiophene. This is the first instance in which organolithium and organocalcium compounds have been observed to metalate the same nucleus in different positions.

By treating 4-dibenzothienyllithium with oxygen, 4-hydroxydibenzothiophene is obtained. This phenol is a solid of melting point 167° and when a concentrated solution of it in alcohol is treated with 1 per cent ferric chloride solution a green color is observed. When a warm acetic acid solution of the phenol is treated with concentrated nitric acid a dinitro derivative is obtained, m.p. 204° (dec.). Methylation of the phenol with methyl sulfate gives 4-methoxydibenzothiophene.

When 4-hydroxydibenzothiophene is treated with sodium bisulfite and concentrated ammonia in the Bucherer reaction, 4-aminodibenzothiophene, m.p. 110°, is obtained. What is perhaps a better synthesis of this amine consists of treating 4-dibenzothienyllithium with bromine and aminating the resulting mixture of crude 4-bromodibenzothiophene and starting material with concentrated aqueous ammonia in the presence of cuprous bromide in a bomb. By this method a satisfactory yield of the amine may be obtained without the necessity of isolating the intermediate bromo derivative. The acetyl derivative is prepared in benzene solution in quantitative yield when the amine is treated with a slight excess of acetic anhydride.

Since it is supposed that the dibenzothiophenecarboxylic acid obtained by metalation with phenylcalcium iodide is the 3-acid, and since the 2- and 4-acids are known, the synthesis of the remaining monocarboxylic acid (the

1-acid) was planned. Our knowledge of the orienting influence of substituents in the dibenzofuran nucleus may be assumed to suffice in the case of dibenzothiophene. Therefore, bromination of 4-acetaminodibenzothiophene should yield 1-bromo-4-acetaminodibenzothiophene. Hydrolysis of the acetamino group followed by diazotization and removal of the amino group would then give 1-bromodibenzothiophene. The Grignard reagent derived from this bromo compound, when carbonated, would then lead to the desired 1-acid.

Actually, the complete synthesis of the 1-acid was not accomplished for lack of time, but bromination of the 4-acetaminodibenzothiophene in acetic acid gave a bromo derivative of sharp melting point in high yield, indicating the absence of isomers. At the time of writing, the remaining steps of the synthesis had not been performed.

Mercuration with mercuric acetate results in the substitution of dibenzofuran in the 4-position and carbazole in the 2-position. Mercuration of dibenzothiophene has not been accomplished in any solvent, but by fusing the reactants together acetic acid is liberated and mercuration evidently takes place. However, no satisfactory acetoxymercuri derivative has been isolated from the reaction in a sufficiently pure state to give a satisfactory analysis. The product which is obtained, when analyzed for mercury, shows a mercury content of about 2 per cent too much. It is believed that this compound is actually acetoxymercuridibenzothiophene which is contaminated with a little dimercurated material.

Dibenzothiophene is best prepared by the action of aluminum chloride on a mixture of sulfur and biphenyl. In a search for various methods of structure proof by synthesis, the possibility of obtaining substituted dibenzothiophenes by applying this reaction to substituted biphenyls was investigated. The polymerizing effect of the catalyst seems quite marked, however, under the conditions necessary to produce an evolution of hydrogen sulfide, and from p-bromobiphenyl the only product which could be isolated after heating with sulfur and aluminum chloride was dibenzothiophene, in 15 per cent yield. A large amount of insoluble, resinous material remained in the reaction flask. The use of a milder condensing agent is apparently not practicable, but there were some indications which point to the success of the method when chlorobiphenyls and a lower temperature are employed. It is felt that this investigation was not as thorough as the possibilities of the reaction deserve.

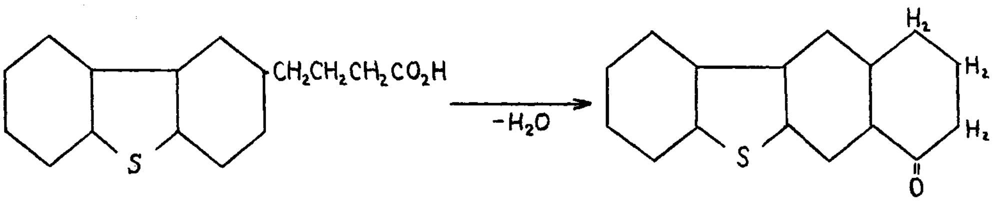
With a view to obtaining alkylated imidazoles which might be found of value for their physiological action, the nitration of 2-acetaminodibenzothiophene was investigated. This compound, which has been previously reported[34] as melting at 168°, was found to melt at 178°. Because of the difficulty of obtaining 2-nitrodibenzothiophene in satisfactory yields for conversion into the desired amine, two new routes to the acetamino derivative were developed. The first involves the bromination of dibenzothiophene, amination of the bromo derivative with strong ammonia in a bomb, and acetylation of the resulting amine. The other method consists of acetylating dibenzothiophene, making the oxime of the resulting ketone, and treating the oxime with phosphorus pentachloride to effect the Beckmann rearrangement to the desired product. The latter method is perhaps the faster, on account of the slow reaction between bromine and dibenzothiophene, and by either method the overall yield of acetamino compound, based on the dibenzothiophene, is at least 38 per cent.

As would be expected from a study of dibenzofuran chemistry, and other considerations, the influence of the acetamino group in the dibenzothiophene nucleus is to facilitate further substitution in the same ring. Therefore, nitrating conditions may be employed sufficiently mild to avoid attack of the sulfide linkage, and by treating with fuming nitric acid in acetic anhydride solution at 20° a 67 per cent yield of a nitro-2-acetamino derivative is obtained, melting at 209°. A small amount of a nitro-aminodibenzothiophene, melting with decomposition at 248-50°, is also produced during the nitration. With a view to obtaining the nitro-amino derivative from the nitro-acetamino compound, in order to prepare the imidazole, the nitro-acetaminodibenzothiophene was refluxed an hour and a half with a mixture of equal volumes of absolute alcohol and concentrated hydrochloric acid. Contrary to expectation, the only product which was isolated was a nitrogen-free material of melting point 88°. Although analyses of this material were carried out, it was not identified and other methods of hydrolysis were not attempted.

The Friedel-Crafts reaction was again employed in the synthesis of polycyclic derivatives to be used for physiological testing. The first of such derivatives to be prepared was a tetrahydrothiobrasan. Calculated amounts of dibenzothiophene and succinic anhydride were suspended in a mixture of tetrachloroethane and nitrobenzene and, while the reaction was kept in an ice bath, anhydrous aluminum chloride was added to effect a condensation to give the dibenzothenoylpropionic acid. In the light of the other Friedel-Crafts reactions with dibenzothiophene, this propionic acid chain is probably in the 2-position of the nucleus. Reduction of the propionic acid derivative to the corresponding butyric acid was accomplished by the method of Clemmensen as modified by Martin[43]. Cyclization of the

(43) Martin, *J. Am. Chem. Soc. 58*, 1438 (1936).

dibenzothienylbutyric acid to the tetrahydrothiobrazan was effected by the use of 88 per cent sulfuric acid. Assuming the side chain before cyclization to have been in position 2, ring closure could lead to either the β- or γ-thiobrazan. There is no evidence to allow us to choose between the two possibilities, the first of which is illustrated in the following reaction.



1-Keto-1,2,3,4-tetrahydrothiobrazan

The Friedel-Crafts condensation between dibenzothiophene and phthalic anhydride, carried out in much the same way as in the case of succinic anhydride, gave what appears to be a hydrate of o-2-dibenzothenoylbenzoic acid. The ethyl ester was prepared and analysed correctly. Treatment of the benzoic acid derivative with sulfuric acid under varying conditions did not lead to ring closure, but the method of Fieser and Fieser[44], using a fusion with aluminum chloride and sodium chloride effected cyclodehydration to the thionaphtheneanthraquinone. The melting point of the crude product gave some evidence that isomers are formed in the cyclization but one product only was isolated after recrystallization from acetic acid or chlorobenzene. As in the case of the thiobrazan, two compounds could be expected to result from ring closure and there is no evidence which permits us to choose one structure as that of the product obtained. The linear compound

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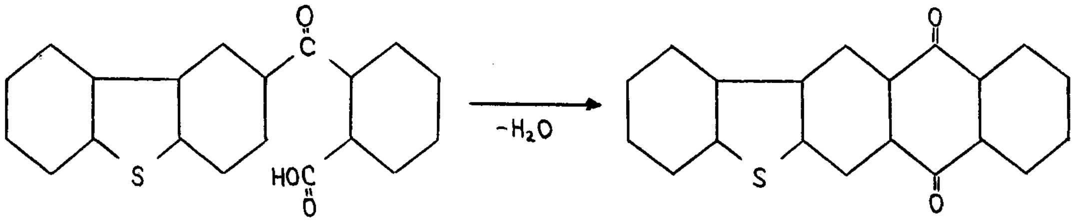
(44) Fieser and Fieser, J. Am. Chem. Soc., 54, 3749 (1932).

is shown in the following reaction.



Sulfoxide and sulfone types. Oxidation of the sulfur atom of dibenzothiophene leads to the sulfoxide (dibenzothiophene-5-oxide) and, finally, to the sulfone (dibenzothiophene-5-dioxide). Very little study has been made of the sulfoxides and their mention will, of necessity, be brief.

When Courtot and Pomonis[34] first sought to nitrate dibenzothiophene they employed a nitrating mixture of 38 parts of nitric acid, 50 parts of sulfuric acid, and 12 parts of water, this mixture having been observed to convert benzene to nitrobenzene in quantitative yield. With dibenzothiophene, however, the previously unknown sulfoxide was the principal product. This sulfoxide was found to behave toward ethylmagnesium bromide like diphenyl sulfoxide, being readily reduced to the original sulfide again. This ease of oxidation of the sulfur linkage made it necessary for Courtot and Pomonis to materially alter the conditions of nitration, and in spite of their control of the reaction the yield of 2-nitrodibenzothiophene never exceeded 40 per cent and an equal yield of the sulfoxide accompanied the desired product.

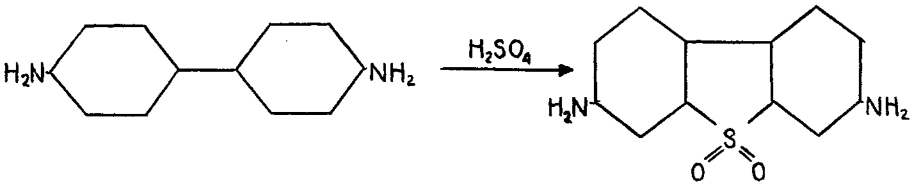
In the most recent article dealing with dibenzothiophene, Courtot[45] has summarized the methods of obtaining dibenzothiophene-5-dioxide as follows:

(45) Courtot and Rochebouet, Bull. soc. chim., (5) 4, 1972 (1937).

1. Oxidation of dibenzothiophene by various oxidizing agents.
2. Removal of the amine groups from benzidine sulfone (3,7-diaminodibenzothiophene-5-dioxide).
3. Cyclization of biphenyl-2-sulfonic acid chloride by means of aluminum chloride.

These methods will be dealt with in the order given above. The first method, involving the oxidation of the sulfur atom, has already been briefly mentioned in connection with the proof of structure of the substitution products arising from halogenation, nitration, etc. Where no substituents are present on the nucleus, or where they are stable enough to withstand the action of the reagents, oxidation is smoothly and rapidly effected by sodium dichromate in dilute sulfuric acid. By this method many of the dibenzothiophene derivatives prepared by Courtot and co-workers have been converted to the corresponding sulfones. In some cases, especially where the nature of the substituents makes it inadvisable to use dichromate and sulfuric acid, oxidation is carried out with hydrogen peroxide. Hydrogen peroxide does not appear to have been used for the preparation of sulfoxide types in any case.

A discussion of the second method referred to by Courtot, involving the removal of amine groups from benzidine sulfone, requires some mention of the latter material at this point. When benzidine is treated with fuming sulfuric acid 3,7-diaminodibenzothiophene-5-dioxide results. This reaction is shown in the following equation:



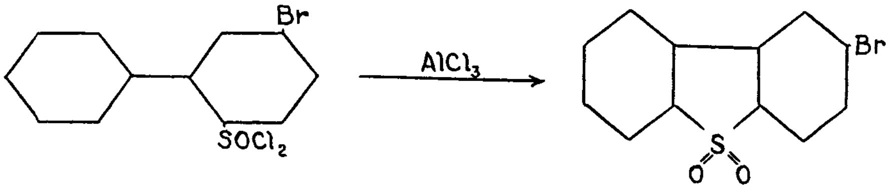
Evidently, in sulfuric acid solution, the positions meta to the amine-salt groups are labilized and sulfonation occurs in one ring, to be quickly followed by cyclodehydration under the influence of the fuming sulfuric acid. The proximity of the 2'-position in the second ring, together with the fact that the amine-salt group has activated it causes ring closure to occur there. That the labilizing group in the second ring is necessary is inferred from the behavior of *p*-xenyl amine under similar conditions. When added to fuming sulfuric acid xenyl amine is sulfonated but continued contact with the sulfuric acid did not result, in our experiment, in the formation of any non-acidic material. Notwithstanding the supposition of Carnelley and Schlesselman[46] that sulfonation occurs in the 4'-position, it is believed quite possible that sulfonation actually occurs in the position meta to the amine-salt group, as in benzidine, and cyclodehydration to the 3-aminodibenzothiophene-5-dioxide fails to take place on account of the absence of a suitable labilizing group in the second ring.

Conversion of the amine groups of benzidine sulfone to other substituents (or to hydrogens) leads to derivatives of dibenzothiophene-5-dioxide in which the substituents are always in the 3- or 3,7-positions, whereas the oxidation of substituted dibenzothiophenes (method 1 above), leads, in most cases, to sulfone derivatives having substituents in the 2-

(46) Carnelley and Schlesselman, *J. Chem. Soc.*, *49*, 380 (1886).

or 2,8-positions.

The third method has already been referred to in the section on the proof of structure of the substitution products resulting from halogenation, etc. This method permits of the synthesis of the four theoretically possible



monosubstituted derivatives of dibenzothiophene-5-dioxide, depending upon which biphenyl-2-sulfonic acid is started with. By it, Courtot[45] reports the synthesis of the first disubstituted dibenzothiophene-5-dioxide having both substituents in the same ring. This is a 2,4-dihalogeno derivative, obtained from the 3,5-dihalogenobiphenyl-2-sulfonic acid.

A fourth route to substituted diphenylene sulfones which was overlooked by Courtot is that reported by Cullinane, Davies, and Davies[47]. By treatment of diphenylene sulfone with fuming nitric acid and concentrated sulfuric acid, these investigators obtained 3,7-dinitrodibenzothiophene-5-dioxide, identified by reduction to benzidine sulfone. The corresponding dibromo derivative was obtained by refluxing diphenylene sulfone in several molecular quantities of bromine. This latter route merits further study in an effort to obtain monosubstitution products through the use of milder conditions.

(47) Cullinane, Davies, and Davies, J. Chem. Soc., 1435-37 (1936).

It will be remembered that all the methods of synthesis of dibenzothiophene derivatives of known constitution for use in proof of structure which have been used by other workers lead to the sulfone types. Because of the frequent high melting points and low solubilities of these diphenylene sulfones, it would be desirable to be able to convert them to the lower-melting sulfides. While the conversion of sulfides to sulfones by strong oxidizing agents is a familiar and smooth reaction, the reverse process is rarely met with. The discovery that diphenylene sulfone can be converted to dibenzothiophene by heating with sulfur was a natural outgrowth of the observation by Courtot[48] that heating a mixture of selenium and diphenylene sulfone yields dibenzoselenophene. A study of the applicability of the reaction between diphenylene sulfone and sulfur to the case in which the diphenylene sulfones bear substituents would be of interest for purposes of structure-proof.

Reduction studies on dibenzothiophene. When dibenzothiophene is treated with sodium in liquid ammonia solution, a dihydro derivative is obtained which, by analogy to the behavior of naphthalene, phenanthrene, and dibenzofuran[49], is probably 1,4-dihydrodibenzothiophene. The dihydro compound, when treated with bromine in chloroform solution at 0°, absorbs a mole of bromine without evolution of hydrogen bromide. Attempts to recrystallize the resulting oil lead to the loss of hydrogen bromide and the formation of dibenzothiophene. The instability of the bromine addition product is analogous to that of the corresponding 1,4-dihydronaphthalene.

(48) Courtot and Motamedi, Compt. rend., 199, 531 (1934); private communication to Dr. Henry Gilman.
(49) C. W. Bradley, Doctoral Thesis, Iowa State College (1937).

When the dihydrodibenzothiophene is treated with phenyllithium under conditions identical with those employed in metalations, dibenzothiophene is obtained in an almost quantitative yield, along with an appreciable quantity of benzene and a solid material which behaves like lithium hydride. This dehydrogenating effect of phenyllithium has been noted also with 1,4-dihydronaphthalene and 1,4-dihydrodibenzofuran[50]. It was subsequently shown that phenyllithium is cleaved by hydrogen in the absence of a catalyst to give benzene and lithium hydride. The readily obtainable phenylisopropylpotassium exerts a similar effect on dihydrodibenzothiophene.

Earlier work on the reduction of organometallic compounds has been done in this country by Adkins[51]. In 1932 he established a series of organometallic compounds in the order of their decreasing ease of reduction as follows: R_2Mg, R_2Zn, R_4Pb. The compound RLi (phenyllithium) was found to apparently undergo reduction with greater facility than reported for the magnesium compound, thus bringing it into this series before the others. This series, it will be noticed, is then in the order of decreasing reactivity as established by other methods[52].

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(50) C. W. Bradley, Unpublished results.
(51) Zartmann and Adkins, J. Am. Chem. Soc., 54, 3398 (1932).
(52) Gilman, "Organic Chemistry", John Wiley and Sons, New York (1938), pp. 406-488.

Results of physiological tests. Because of the time required for the testing of the dibenzothiophene derivatives submitted, especially those tested for estrogenic and carcinogenic activity, the results given here are not complete.

Tests on dibenzothiophene-4-carboxylic acid, 1-keto-1,2,3,4-tetrahydrothiobrazan, and 2-acetaminodibenzothiophene failed to show any analgesic action when the compounds were administered intraperitoneally to white mice or orally to guinea pigs, although there was slight evidence of hypnotic action in the acetamino compound. The minimum lethal dose (M.L.D.) of each compound was found to be 0.15 mg. per g. of body weight for mice.

Tests on 2-aminodibenzothiophene and the dihydrochloride of benzidine sulfone showed no indication of any antistreptococcic activity. In these tests the compounds were given orally to white mice infected with *Streptococcus hemolyticus*. The M.L.D. for the dihydrochloride of benzidine sulfone, under these conditions was found to be 1.25 mg. per g.

The following compounds were found to possess no estrogenic activity when 25 mg. of the substance was injected subcutaneously in sesame oil:

(a) 1,4-dihydrodibenzothiophene
(b) dibenzothiophene
(c) 1-keto-1,2,3,4-tetrahydrothiobrazan

Five mice were used for each compound.

EXPERIMENTAL

Preparation of Dibenzothiophene.

Dibenzothiophene was prepared essentially according to a method outlined in the patent literature[32]. In a typical preparation, 500 g. of technical biphenyl and 208 g. of sulfur were melted together in a 5-L. round-bottomed flask, immersed in an oil bath. While the temperature of the bath was maintained at 115-120°, 25 g. of powdered, anhydrous aluminum chloride was added over a period of one and a quarter hours. The temperature was kept the same until the end of the third hour and then gradually allowed to rise, reaching 240° at the end of the eighth or ninth hour. When cool, the mass in the reaction flask was extracted three times by boiling gently with 500 cc. of water, cooling, and decanting the water. Then eight alcohol extractions were made, boiling each time with a liter of alcohol and decanting hot. The combined extracts were digested with norite and filtered through a hot Büchner funnel immediately. Upon cooling, almost colorless needles separated from the filtrate. Concentration of the liquors yielded additional dibenzothiophene. This crude compound usually melts as high as 98° and is suitable for many purposes. Yield, 65-70 per cent of the theoretical. Distillation in vacuum (b.p. 152-154°/3 mm.) followed by crystallization from alcohol gives beautiful colorless needles, m.p. 99°.

Picrate of Dibenzothiophene.

One gram (0.005 mole) of dibenzothiophene dissolved in 20 cc. of hot alcohol was treated with a hot solution of 1.4 g. (0.006 mole) of picric acid in 11 cc. of alcohol. Upon cooling, 1.1 g. of yellow needles, m.p. 124-125°, separated. Recrystallization from alcohol gave yellow needles, constant m.p.

of 125°.

Reaction of Sulfur with Dibenzothiophene-5-dioxide.

In a 25-cc. Claisen flask was placed 5 g. (0.023 mole) of dibenzothiophene-5-dioxide and 0.9 g. (0.028 g.-atom) of sulfur. A thermometer was dipped into the reaction mixture and the flask heated in a metal bath. The mass melted at 160-200° and was kept at 320° for 2½ hours while sulfur dioxide and hydrogen sulfide were evolved. The temperature was then raised to 340° for another half hour, causing gentle boiling, and then heating was increased until 2.3 g. of distillate was collected, m.p. 94-95°. This was recrystallized and identified (mixed melting point) as dibenzothiophene. Yield 54 per cent.

Preparation of 2-Acetyldibenzothiophene.

In a 500-cc. three-necked flask was placed 30 g. (0.16 mole) of dibenzothiophene, 225 cc. of dry carbon disulfide, and 60 g. of powdered, anhydrous aluminum chloride. With stirring 13 g. (0.16 mole) of acetyl chloride was added dropwise over a 20-min. period, causing gentle refluxing of the solvent. After addition was complete the mixture was heated and stirred for two hours longer, then cooled and poured over a kilogram of ice-HCl. Nearly all the mixture was soluble in the two layers. Insoluble material was removed by filtration and the carbon disulfide layer was separated and thoroughly washed with water and sodium bicarbonate solution and then dried over sodium sulfate. After drying, the carbon disulfide solution was freed of solvent and the residue distilled under reduced pressure from a small Claisen flask. A small forerun (1-2 g.) was taken off below 170°/1-2 mm., and the product, which distilled as a pinkish, slow-crystallizing liquid, was collected between

170° and 196° at 1-2 mm., the larger part of the fraction distilling at 193-196°. Weight 25 g. or about 70 per cent yield. Recrystallization from alcohol gives a product suitable for most purposes (m.p. 108-109°) but several more recrystallizations will give a product melting at 111°.

Anal. Calcd. for $C_{14}H_{10}OS$: S, 14.2. Found: S, 14.1.

Oxime of 2-Acetyldibenzothiophene.

The method of oximation of Bachmann and Boatner[53] was employed. The ketone (48.5 g. or 0.215 mole) was treated with 31.2 g. (0.45 mole) of hydroxylamine hydrochloride in a mixture of 150 cc. of absolute alcohol and 60 cc. of pyridine, by refluxing for 3 hours. About half the solvent was then evaporated off and the mixture poured into 800 cc. of cold water. A nearly quantitative yield of crude oxime results, which is dried and recrystallized from alcohol. M.p. pure oxime, 160-161°.

Anal. Calcd. for $C_{14}H_{11}ONS$: N, 5.81. Found: N, 5.55 and 5.59.

Oxidation of 2-Acetyldibenzothiophene.

Using the method of Fuson and Tullock[41], one gram of 2-acetyldibenzothiophene was dissolved in 50 cc. of technical dioxane and 10 cc. of 10 per cent sodium hydroxide solution was added. Iodine-KI solution was added in accordance with the prescribed procedure until a brown color was persistent for one minute at 60°. Excess sodium hydroxide solution was then added and the solution cooled and filtered from the iodoform. The filtrate was extracted once with ether and acidified with hydrochloric acid to precipitate 0.15 g. of acid which was recrystallized from methanol, m.p. 253°. Treatment with diazomethane gave the methyl ester, m.p. 75°, which gave no depression in

(53) Bachmann and Boatner, J. Am. Chem. Soc., 58, 2099 (1936).

melting point when mixed with authentic methyl dibenzothiophene-2-carboxylate.

Preparation of 2-Bromodibenzothiophene.

This compound was originally prepared by Courtot[35] but since the preparative procedure was not published it is given here. Dibenzothiophene (18.4 g. or 0.1 mole) was dissolved in 75 cc. of carbon tetrachloride and a pinch of powdered aluminum chloride was added. While the solution was stirred and gently heated, 16 g. (0.1 mole) of bromine was added dropwise over a two-hour period. Heating and stirring were continued for 24 hours longer. The mixture was then cooled, washed free of excess bromine with a bisulfite wash, and the carbon tetrachloride solution was then carefully washed with sodium carbonate and water and dried over sodium sulfate. After evaporation of the solvent, the product was distilled under reduced pressure and recrystallized to give a 54 per cent yield (14 g.) of 2-bromodibenzothiophene, m.p. 124-125°. Considerable loss results in the recrystallization and if a less pure product is usable (as for example, in amination), the yields are considerably higher, in the neighborhood of 70 per cent.

Preparation of Dibenzothiophene-2-carboxylic Acid from 2-Bromodibenzothiophene.

This acid was first described by Courtot[35] but the details of the preparation were not published. Nine and two-tenths grams (0.05 mole) of 2-bromodibenzothiophene was placed in a 250-cc. three-necked flask with 100 cc. of dry ether and 1.5 g. of powdered magnesium. Heat was applied to the mixture with stirring, and was continued until about 3-4 hours after the mixture had become clear. Loss of turbidity, indicating the onset of the reaction, occurs in a period from one-half hour to 24 hours after the start of heating, depending upon catalysts used. Best results were obtained when magnesium activated by heating with iodine was added to the magnesium already in the flask. When cool, the Grignard solution is carbonated with solid carbon dioxide. After removal of the dry ice, dilute sodium hydroxide was added, the ether was evaporated, and the mixture filtered. Acidification of the alkaline filtrate gave 1.35 g. of dibenzothiophene-2-carboxylic acid, m.p. 255°. This is a 17 per cent yield.

Preparation of Methyl Dibenzothiophene-2-carboxylate.

Treatment of the dibenzothiophene-2-carboxylic acid obtained by Courtot's method from the corresponding bromo derivative with excess diazomethane gave an oil which slowly crystallized. Recrystallization of this ester from methanol gave methyl dibenzothiophene-2-carboxylate, m.p. 74-75°.

Anal. Calcd. for $C_{14}H_{10}O_2S$: S, 13.2. Found: S, 13.5

Preparation of Dibenzothiophene-4-carboxylic Acid by Metalation.

A. With *n*-butyllithium: Ten grams (0.054 mole) of dibenzothiophene was metalated by treating it in 75 cc. of ether with nearly 0.1 mole of *n*-butyllithium in 75 cc. ether. The reaction mixture was refluxed gently for 15 hours and then carbonated by pouring over solid carbon dioxide. After removal of the excess carbon dioxide the mixture was extracted with water and the water layer acidified with hydrochloric acid to yield 6.7 g. of white solid, melting from 235 to 245°. Yield of crude acid 54 per cent. Two recrystallizations from methanol gave a white product melting at 252-253°.

Anal. Calcd. for $C_{13}H_8O_2S$: N.E., 228.1; C, 68.38; H, 3.54; S, 14.1. Found: N.E., 237; C, 68.18; H, 3.80; S, 14.0.

B. With phenyllithium: Ten grams of dibenzothiophene, metalated as above, but using this time phenyllithium, in about the same excess, gave, upon carbonation, a 12 per cent yield of dibenzothiophene-4-carboxylic acid. Even more strikingly, in the case of phenyllithium, is shown the necessity of using distilled dibenzothiophene in the metalation. When using butyllithium the use of dibenzothiophene as obtained directly from the alcohol extracts, before distillation, results in a greatly diminished yield. In the case of phenyllithium the yield is reduced to almost nothing. Probably the low yields are due to the presence of sulfur in the dibenzothiophene which has not been distilled and recrystallized.

C. With α-naphthyllithium: Metalation of redistilled dibenzothiophene with a large excess of α-naphthyllithium results in the formation of only a 7.6 per cent yield of dibenzothiophene-4-carboxylic acid. The latter is readily freed from naphthoic acid by treatment with boiling water in which dibenzothiophene-4-carboxylic acid is insoluble.

D. With *p*-anisyllithium: The preparation of *p*-anisyllithium was carried out in the manner customary for the organolithium compounds by adding 28 g. (0.15 mole) of *p*-bromoanisole in 30 cc. of ether to 2.1 g. (0.30 g.-atom) of finely cut lithium in 45 cc. of ether at a rate sufficient to cause steady boiling. After addition was complete, stirring was continued for 30 minutes longer without heating. The ether solution was then strained free of unreacted metal into another flask containing 15 g. (0.082 mole) of dibenzothiophene in 75 cc. of ether. The reaction mixture was then refluxed for 20 hours and carbonated by pouring onto solid carbon dioxide. Working up the resulting mixture in the usual way gave, upon acidification of the alkaline, aqueous layer, a precipitate of colorless crystals. After one recrystallization from boiling water the acidic material melted at 120-121° and weighed 2.2 g. Qualitative tests for sulfur were negative and a mixed melting point with benzoic acid was depressed. No sparingly soluble dibenzothiophenecarboxylic acid was found. Another identical run gave 5.2 g. of the above acid melting at 118-120° before recrystallization. As before, no dibenzothiophene acid was obtained.

Since no metalation of the dibenzothiophene occurred with p-anisyllithium, the expected acid would be p-anisic acid. When the acid actually obtained was found not to correspond to any of the anisic acids, a further investigation of the reaction was undertaken. p-Anisyllithium was prepared as described above and carbonated immediately after the thirty-minute period of stirring at room temperature. Working up the reaction mixture in the usual way then gave 2 g. of acid, m.p. 182-182.5° after recrystallization from water. A mixed melting point with authentic p-anisic acid showed no depression. Yield of p-anisic acid, 8.7 per cent of the theoretical. From the ether layer of the reaction mixture was obtained 2.2 g. of 4,4'-dimethoxybenzophenone, m.p. 144°. This ketone was identified further by the oxime, which was found to melt at 133°, in agreement with the literature[54]. Yield of ketone, 12.2 per cent of the theoretical.

Having thus shown that p-anisyllithium actually is formed in the reaction between p-bromoanisole and lithium, another run was made to determine what effect, if any, would be found by refluxing the ether solution of the organolithium compound, as was done in the metalation experiments. This preparation was carried out with the same quantities of materials as used in the preceding runs. After the period of stirring at room temperature, the ether solution was strained free of metal into a second flask and diluted with 75 cc. of ether. It was then refluxed for 21 hours and

(54) Schnackenberg and Scholl, Ber., 36, 654 (1903).

carbonated and worked up as before. Yield of crude acid, 5.2 g. A small amount of oily material was obtained from the ether layer but attempts to cause it to crystallize were futile. The acidic material was recrystallized from water and found to be the same acid, of m.p. 120-121°, as obtained in the metalation experiments. Neutral equivalent determinations gave values of 201 and 202. The acid has not yet been identified.

Decarboxylation of Dibenzothiophene-4-carboxylic acid.

About 0.1-0.2 g. of the acid was mixed with an equal quantity of copper powder and 2-3 cc. of quinoline and heated in a test tube immersed in a metal bath. Gas evolution was apparent at 120°. The bath was kept at about 200° for an hour. The reaction mixture was then cooled and transferred to a 125-cc. distilling flask, with 2-3 cc. of concentrated sulfuric acid and 40-50 cc. of water. Distillation yielded a crystalline solid in the distillate, m.p. 97-98°, mixed melting point with authentic dibenzothiophene the same.

Preparation of Methyl Dibenzothiophene-4-carboxylate.

Treatment of 0.2-0.3 g. of dibenzothiophene-4-carboxylic acid with excess diazomethane in ether, and allowing the reaction mixture to stand over night, gave the methyl ester, m.p. 95° after two recrystallizations from methanol.

Anal. Calcd. for $C_{14}H_{10}O_2S$: S, 13.2. Found S, 13.1.

Preparation of 4-Methyldibenzothiophene.

A. By metalation: *n*-Butyllithium was prepared in ether solution in the usual way by adding 205.5 g. (1.5 mole) of *n*-butyl bromide in 300 cc. of dry ether to 21 g. (3 g.-atoms) of finely cut lithium in 500 cc. of ether. This solution was then transferred through a strainer of glass wool to another flask containing 140 g. of dibenzothiophene in 400 cc. of ether. The reaction mixture was refluxed and stirred over night and then cooled in an ice bath while 126 g. (1 mole) of dimethyl sulfate in 100 cc. of ether was slowly added. Stirring the mixture for an additional thirty minutes at room temperature completed the reaction so that a color test was negative. Excess dimethyl sulfate was destroyed by the cautious addition of 500 cc. of 10 per cent sodium hydroxide solution, followed by stirring for a few hours at room temperature. The ether layer was then separated, washed with dilute hydrochloric acid and with water, and dried over calcium chloride. The extract was then freed of the ether and the residual solid distilled under reduced pressure. Thirty grams of solid was collected at 147-150°/2-3 mm. and 20 grams was collected at 150-155° at the same pressure. While both fractions undoubtedly contained the methyl derivative, only the higher-boiling one was worked up. By taking this fraction up in alcohol and allowing the dibenzothiophene to crystallise out slowly, the liquors could be made to yield crude 4-methyldibenzothiophene of m.p. 54-55°. Recrystallization from dilute methanol gave a product of m.p. 65°.

__Anal__. Calcd. for $C_{13}H_{12}S$: S, 16.0. Found: S, 16.1.

B. By ring closure: In a small Claisen flask was placed a mixture of 2 g. of 3-methyl-2,2'-dihydroxybiphenyl and 1 g. of phosphorus pentasulfide. The flask was heated in a metal bath, the temperature being gradually raised from 165° (at which evolution of hydrogen sulfide began) to 400° in 45 minutes, after which heating was increased until a small amount of colorless liquid distilled. The liquid solidified and was recrystallized once from a little methanol to give small needles, m.p. 66.5°. A mixture of this material with the methyldibenzothiophene obtained by metalation (see above), m.p. 65°, melted at 65.5°.

Preparation of Dibenzothiophene-3-carboxylic acid.

Phenylcalcium iodide was made in the customary manner using 122.4 g. (0.6 mole) of iodobenzene, 48 g. (1.2 g-atom) of calcium turnings, and 300 cc. of ether. After the preparation, the mixture was allowed to settle over night and then the ether solution of phenylcalcium iodide was decanted into a 1-L. flask containing 27.6 g. (0.15 mole) of dibenzothiophene and 250 cc. of ether. The mixture was then refluxed gently for 24 hours and carbonated with solid carbon dioxide. After removal of excess carbon dioxide the mixture was treated with 200 cc. of dilute hydrochloric acid and extracted with ether. The combined ether extracts were then extracted with dilute sodium hydroxide solution and the acidic materials precipitated from this by acidification with hydrochloric acid. The heavy precipitate of yellow acidic material was digested with 600 cc. of boiling water and filtered hot, leaving the desired dibenzothiophene acid on the filter. This brownish acid weighed three grams and was recrystallized from methanol to give an almost white solid which appeared to decompose or decarboxylate at about 300-305°, but which had no sharp melting point.

Neutral equivalent: Calcd, 228. Found, 234.

Decarboxylation of Dibenzothiophene-3-carboxylic Acid.

About 0.1-0.2 g. of the acid was heated in 2-3 cc. of quinoline at 200° with an equal amount of copper powder for an hour. Evolution of gas was noticed as low as 120°. The mixture was then cooled and transferred to a small distilling flask where it was mixed with 40-50 cc. of water and 2-3 cc. of concentrated sulfuric acid. Distillation gave a yellowish, crystalline solid in the distillate which, after sublimation, melted at 97-98° and gave no depression with authentic dibenzothiophene.

Preparation of Methyl Dibenzothiophene-3-carboxylate.

One-half gram of the acid obtained from metalation with phenylcalcium iodide was treated with a large excess of diazomethane in ether and allowed to stand over night in the refrigerator. Evaporation of the ether then left a white solid which was taken up in alcohol, treated with norite, and filtered hot. From the filtrate deposited small, colorless crystals, m.p. 128°. Another recrystallization of this ester from a mixture of methanol and ethanol (1:2) gave a colorless product, m.p. 129-130°.

Anal. Calcd. for $C_{14}H_{10}O_2S$: S, 13.2. Found: S, 13.1.

Preparation of 4-Hydroxydibenzothiophene.

One-half mole of dibenzothiophene was metalated in the usual way with an ether solution of n-butyllithium prepared from 1.5 moles of n-butyl bromide and 3 g.-atoms of lithium. After the metalation was completed, 0.5 mole of ethylmagnesium chloride in 500 cc. of ether was added, the flask was immersed in a freezing mixture, and oxygen was led in over the stirred surface at about 10 mm. head of pressure. The temperature was kept below 3° by regulating the intake of oxygen and a negative color test after 5 hours showed that reaction was complete. The reaction mixture was transferred to a large separatory funnel with about 600 cc. of water containing 150 cc. of concentrated hydrochloric acid. The water layer was discarded and the ether layer washed with water. The product was then extracted from the ether solution by several washings with 5 per cent sodium hydroxide solution. The combined alkaline extracts were then digested warm with norite, filtered, and acidified with hydrochloric acid. Yield of almost white product, 33 g. or 33 per cent of the theoretical. Melting point, 157-159°. Recrystallization from dilute methanol gave fine, colorless needles, m.p. 167°. A green color is obtained with ferric chloride solution.

Anal. Calcd. for $C_{12}H_8OS$: S, 16.0. Found: S, 15.9.

Preparation of Dinitro-4-hydroxydibenzothiophene.

One-half gram of 4-hydroxydibenzothiophene was dissolved in 8 cc. of glacial acetic acid at about 50°. To this was added a mixture of 2 cc. of glacial acetic acid and 1.3 cc. of concentrated nitric acid. The reaction mixture became dark red and a dark, crystalline precipitate separated immediately. The mixture was cooled and filtered to yield a dark orange, crystalline powder, m.p. 204° (dec.). Recrystallization from glacial acetic acid did not raise the melting point. Yield 0.56 g. or 77 per cent of the theoretical.

Anal. Calcd. for $C_{12}H_6O_5N_2S$: N, 9.65. Found: N, 9.45.

Preparation of 4-Methoxydibenzothiophene.

In a 250-cc. flask was placed a solution made from 100 cc. of water, 3.5 g. (0.088 mole) of sodium hydroxide, and 15 g. (0.075 mole) of 4-hydroxydibenzothiophene. With cooling, 12.6 g. (0.1 mole) of dimethyl sulfate was added over a 5-minute period with stirring. Stirring was then continued 25 minutes after which the flask was immersed in a bath of boiling water and 2 g. of sodium hydroxide was added to destroy the excess dimethyl sulfate, thirty minutes being allowed for this. Cooling and filtering then gave 15 g. or a 94 per cent yield of crude methoxy compound.

Two recrystallizations from alcohol gave heavy, colorless needles, m.p. 123°.

Anal. Calcd. for $C_{13}H_{10}OS$: S, 15.0. Found: S, 14.9.

Preparation of 4-Aminodibenzothiophene.

A. By the Bucherer reaction: Following a procedure for the Bucherer reaction given by Fieser and co-workers[55], 1.5 g. of 4-hydroxydibenzothiophene, 7.5 g. of sodium bisulfite, 15 cc. of water, 15 cc. of concentrated aqueous ammonia, and 7.5 cc. of dioxane were sealed up in a Carius tube and heated for 11 hours at 200-210°. Upon opening the tube no pressure was found and there was no evidence of darkening of the contents. The mixture was transferred to a separatory funnel with a little more than an equal volume of water and the mixture extracted with ether. The ether extracts were combined, washed, and dried over solid sodium hydroxide. When dry, the ether solution was saturated with dry hydrogen chloride, causing the precipitation of 0.4 g. (23 per cent yield) of almost white amine hydrochloride. After one recrystallization of the hydrochloride the free base was obtained by treatment with ammonia. Melting point, 110°. Recrystallization of the amine from methanol failed to raise the melting point.

Anal. Calcd. for $C_{12}H_9NS$: N, 7.04. Found: N, 7.02.

B. By amination of 4-bromodibenzothiophene: Ninety-two grams (0.5 mole) of dibenzothiophene was metalated with n-butyllithium as in the preparation of 4-hydroxydibenzothiophene. The mixture was then cooled in an ice-salt bath while nitrogen was passed slowly over the stirred surface. The nitrogen first passed through a washbottle containing about 80 g. of bromine, and a slight pressure was maintained on the system by allowing the

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(55) Fieser and co-workers, J. Am. Chem. Soc., 59, 478 (1937).

excess nitrogen to escape through the condenser against a 10-mm. head of mercury. In two and one-half hours the reaction was complete, as indicated by a negative color test. The product was obtained in ether solution, excess bromine was removed by a bisulfite wash, and the ether solution was freed of solvent by distillation. The crude product remaining weighed 90 g. The 4-bromodibenzothiophene was not separated from the contaminating dibenzothiophene but was aminated directly in portions as described below.

Into a steel bomb of about 500-cc. capacity was introduced 25 g. of crude 4-bromodibenzothiophene, 20 g. of freshly prepared cuprous bromide, and 500 cc. of concentrated aqueous ammonia. The bomb was heated for 10-11 hours at 210-220°. When cool, the contents were transferred to a separatory funnel and extracted with ether. The washed and dried ether extract gave 8.3 g. of amine hydrochloride when saturated with dry hydrogen chloride. This crude salt represented a yield of 37 per cent of the theoretical on the basis that the starting material was pure 4-bromodibenzothiophene. The free base was obtained by treating the crude hydrochloride with aqueous ammonia. The crude amine thus produced was recrystallized by treating a hot methanol solution with norite and a pinch of sodium hydrosulfite (to prevent darkening by oxidation). The methanol solution was then filtered hot and diluted with hot water just to the point of turbidity. Slow cooling gave a colorless product which was identical with that obtained by the Bucherer reaction on 4-hydroxydibenzothiophene.

Preparation of 4-Acetaminodibenzothiophene.

In 200 cc. of benzene was dissolved 8.7 g. of 4-aminodibenzothiophene. An excess (10 cc.) of acetic anhydride was then added and the solution allowed to stand over night. The white, crystalline acetamino derivative which separated was obtained in almost quantitative yield. Recrystallization from benzene gave a product of constant melting point, 198°.

Anal. Calcd. for $C_{14}H_{11}ONS$: N, 5.82. Found: N, 5.93.

Bromination of 4-Acetaminodibenzothiophene.

Five grams (0.021 mole) of 4-acetaminodibenzothiophene was dissolved in 175 cc. of glacial acetic acid and treated with 22 cc. of a 0.1 molar solution of bromine in acetic acid. The addition required 30 minutes and the solution was then stirred an additional hour before pouring into 800 cc. of water to which a little sodium bisulfite had been added. The white, precipitated solid weighed 5.75 g. and represented an 86 per cent yield. Two recrystallizations gave a pure product melting at 254°.

Anal. Calcd. for $C_{14}H_{10}ONSBr$: N, 4.38. Found: N, 4.28.

Mercuration of Dibenzothiophene.

Two attempts to mercurate dibenzothiophene by refluxing an alcoholic solution of dibenzothiophene and mercuric acetate gave no mercurial. Mercurous acetate was formed to some extent and a large proportion of the original dibenzothiophene was recovered unchanged.

Mercuration appeared to be effected when the calculated quantity of mercuric acetate was slowly added to a melt of dibenzothiophene at 140-145°. A liquid, having the odor of acetic acid, distilled out of the reaction mass. The melt was stirred and heated for 1½-2 hours and then poured into hot propanol, in which it formed a milky suspension. If the mass is allowed to cool before pouring into the solvent it becomes extremely viscous but does not harden. The milky suspension was filtered while hot and from the milky filtrate a white solid separated upon cooling. This solid, which was probably crude mercurial, was obtained on a filter. Upon standing, it changed to an amber, glassy resin. A more stable solid was obtained when the material precipitated from the propanol was digested briefly with boiling chloroform. The curdy, white solid dissolves in the chloroform upon continued boiling and will not separate when the solution is cooled. Therefore, digestion was only continued long enough to coagulate the solid material and then discontinued. This material melted with decomposition at 215° and was analyzed as follows.

Anal. Calcd. for $C_{14}H_{10}O_2SHg$: Hg, 45.3. Found: Hg, 47.7 and 48.5.

Reaction of Sulfur and p-Bromobiphenyl in the Presence of Aluminum Chloride.

A melted mixture of 11.7 g. (0.05 mole) of p-bromobiphenyl and 3.2 g. (0.1 g.-atom) of sulfur was treated with 0.5 g. of powdered, anhydrous aluminum chloride at 110°. A vigorous evolution of hydrogen sulfide occurred and heating was conducted in the same way as described for the preparation of dibenzothiophene. The cooled mass was extracted three times by boiling with 20 cc. of water, cooling, and decanting the water. The mass was then extracted four times by boiling with 25-cc. portions of alcohol and decanting hot. From the combined alcoholic extracts, after treatment with norite and filtration, was obtained 2 g. (a 15 per cent yield) of dibenzothiophene, identified by a mixed melting point. A large quantity of a tarry material remained in the reaction flask after the alcohol extractions and this was extracted further with benzene but no solid material could be obtained from the benzene extracts.

Other Attempted Reactions between Sulfur and Substituted Biphenyls in the Presence of a Catalyst.

Using the same amounts of sulfur and p-bromobiphenyl as in the preceding experiment, the effect of other condensing agents was investigated. When 0.5 g. of anhydrous zinc chloride was used no evolution of gas could be detected. When 1 g. of anhydrous stannic chloride was tried the same result was obtained. The use of 0.5 g. of anhydrous ferric chloride caused some reaction and the evolution of both hydrogen sulfide and hydrogen halide, but, when the reaction was carried out in the manner described above, no product was obtained except a tarry material.

When a mixture of 9.5 g. (0.05 mole) of o-chlorobiphenyl and 3.2 g. (0.1 g.-atom) of sulfur was treated with 0.5 g. of aluminum chloride as outlined in the first experiment with p-bromobiphenyl, no solid product was obtained.

An equally discouraging result was obtained when the reaction was tried using p-chlorobiphenyl, sulfur, and aluminum chloride. Hydrogen sulfide and hydrogen chloride were copiously evolved and the only product was a tarry mass. However, when the same reactants were employed but heating was done on the steam bath (8 hours), the alcoholic extract of the reaction mixture yielded sulfur and a white crystalline solid. The sulfur separated first and the white solid was obtained by concentration of the liquors. It was found to melt at 170-200°. On account of the dwindling amount of material in hand this was not further investigated but it appears highly possible that, by keeping the temperature of the reaction low enough and by a suitable choice of solvents for recrystallization, the desired 3-chlorodibenzothiophene might be obtained.

Preparation of 2-Acetaminodibenzothiophene.

A. By nitration, reduction, and acetylation: This is the way in which Courtot and Pomonis[34] first prepared the 2-acetaminodibenzothiophene but, since the experimental details were not published by those authors, and since the melting point which was obtained in their work does not agree with that which is given here, the method of synthesis will be described. Dibenzothiophene was nitrated according to the directions of Courtot and Pomonis[34] and the resulting 2-nitrodibenzothiophene reduced to 2-aminodibenzothiophene by treating a suspension of the amine in alcoholic ammonia with zinc dust and ammonium chloride. A solution of 1.5 g. of the amine thus obtained, in 50 cc. of benzene, was treated with 1 cc. of acetic anhydride. Upon standing, the acetamino derivative separated and was filtered out. Melting point, after one recrystallization from benzene, 178°.

Anal. Calcd. for $C_{14}H_{11}ONS$: N, 5.81. Found: N, 5.64 and 5.72.

B. By amination of 2-bromodibenzothiophene followed by acetylation: Into a Carius tube was introduced 2 g. of 2-bromodibenzothiophene, 2 g. of cuprous bromide, and 15 cc. of concentrated aqueous ammonia. The tube was sealed and heated for 8 hours at 200-225°. When cool the contents of the tube were washed out, extracted with ether, and the ether extract washed and saturated with gaseous hydrogen chloride. The precipitated amine hydrochloride weighed 1.1 g. and represented a 62 per cent yield. By digesting the hydrochloride with aqueous ammonia the free amine was obtained. After recrystallization from methyl alcohol it melted at 129° and was shown to be identical with the amine obtained by reduction of the nitro derivative, by the method of mixed melting point. Acetylation was carried out as described above.

C. By the Beckmann rearrangement of the oxime of 2-acetyldibenzothiophene: In 500 cc. of dry benzene, warmed to about 40°, was suspended 40 g. of the oxime. Then an equal quantity of powdered phosphorus pentachloride was added rapidly, causing boiling of the benzene. When the boiling appeared to subside but before the phosphorus pentachloride was all dissolved the mixture was poured over ice, made alkaline with sodium carbonate, and the benzene steam-distilled off. A quantitative yield of crude acetamino compound resulted which, when recrystallized from benzene with the addition of a few drops of acetic anhydride to reconvert any free base to the acetyl derivative was white and melted at 178°. The yield of pure acetaminodibenzothiophene was above 70 per cent.

Nitration of 2-Acetaminodibenzothiophene.

Twenty grams (0.083 mole) of 2-acetaminodibenzothiophene was dissolved in 800 cc. of acetic anhydride by warming slightly and then cooling to 25°. Some solid separated during the cooling. Then with stirring, 15 cc. (0.36 mole) of fuming nitric acid (d. = 1.5) was added, keeping the temperature at 25-27°. The addition required 5 minutes. The red solution was then allowed to stand 25 minutes and then poured into about 3-L. of ice and water. After slow hydrolysis of the acetic anhydride, the solid product was obtained on a Büchner funnel and pressed as dry as possible. It was then recrystallized from methanol, with the use of a little norite. Yield of nitro-acetamino compound, m.p. 208.5-209°, 16 g. or 67 per cent. In several runs, a less soluble material separated first from the methanol, and was obtained as yellow needles, melting point after recrystallization from acetic acid, 250° (dec.). This material, which gave an analysis for a nitro-amino compound, was obtained in 3-4 per cent yield.

Anal. (Compound, m.p. 208.5-209°): Calcd. for $C_{14}H_{10}O_3N_2S$: N, 9.79. Found: N, 9.74 and 9.80. (Compound, m.p. 260°): Calcd. for $C_{12}H_8O_2N_2S$: N, 11.5. Found: N, 11.3 and 11.6.

Attempted Hydrolysis of Nitro-2-acetaminodibenzothiophene.

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Five-tenths of a gram of nitro-2-acetaminodibenzothiophene (m.p. 208.5-209°) was refluxed for one and one-half hours in a mixture of 20 cc. of absolute alcohol and 20 cc. of concentrated hydrochloric acid. At the start all of the material was in solution but gradually the mixture became turbid. An odor somewhat resembling acetaldehyde was noticeable at the top of the condenser. The mixture was next poured into cold water, made alkaline with ammonium hydroxide, and the reddish solid filtered out. This was digested in methanol with norite and filtered hot. The filtrate deposited yellow needles upon cooling, m.p. 85-86°. Two recrystallizations from dilute acetic acid gave a colorless product melting at 88°. Several qualitative tests for nitrogen, including combustion in the micro-Dumas apparatus, were all negative.

Anal. Found: S, 22.4 and 22.4; C, 65.74 and 65.78; H, 3.29 and 3.32.

Preparation of β-2-Dibenzothenoylpropionic Acid.

In a 3-L. three-necked flask was placed 92 g. (0.5 mole) of dibenzothiophene and 55 g. (0.55 mole) of succinic anhydride, suspended in a mixture of 400 cc. of tetrachloroethane and 200 cc. of nitrobenzene. The flask was immersed in a deep ice bath, and the temperature of the reaction mixture was measured by a thermometer dipping into the solvent. With stirring, 150 g. (1.1 mole) of powdered, anhydrous aluminum chloride was added over a period of an hour. The reaction mixture was stirred at 0-5° for 5 hours, packed in ice over night without stirring, and then stirred again the next day at 0-5° for 12 hours. Hydrolysis was then effected at as low a temperature as possible (0-25°) with 250 g. of ice and 150 cc. of concentrated hydrochloric acid. The mixture was then steam-distilled until 450 cc. of mixed solvent had been collected. The residue was then chilled to solidify the cake, the water was decanted, and 55 g. of sodium carbonate in 300 cc. of water was added and steam-distillation renewed until nearly all the organic solvents had been removed. The mixture was then filtered and the filtrate digested with norite for several hours and refiltered. Acidification of the filtrate with hydrochloric acid gave a copious gummy precipitate which slowly hardened and was recovered on a filter. It was redissolved in sodium carbonate solution and treated again with norite, filtered, and reprecipitated. The crude product, when dry, was almost white and weighed 112 g. (m.p. 150-155°). It was recrystallized from a large volume of ethyl acetate to give 74 g. or a 66 per cent yield of pure product melting at 160.5-161°.

Anal. Calcd. for $C_{16}H_{12}O_3S$: N.E., 284.2; S, 11.3. Found: N.E., 285; S, 11.1.

Preparation of γ-2-Dibenzothienylbutyric Acid.

The procedure of Martin[43] was used for this reduction. Fifty grams of mossy zinc was amalgamated by his method and placed in a 1-L. three-necked flask. Then 25 g. of the dibenzothenoylpropionic acid was added, along with 38 cc. of water, 88 cc. of concentrated hydrochloric acid, 75 cc. of toluene, and 3 cc. of glacial acetic acid. The mixture was brought to a boil and refluxed for 30 hours. At approximately 6-hour intervals, three

25-cc. portions of concentrated hydrochloric acid were added through the condenser. After refluxing was stopped the toluene was removed by steam distillation and the mixture allowed to cool. The cake was broken up, dried, and recrystallized from dilute methanol. Yield of colorless needles, m.p. 131°, 16 g. or 67 per cent of the theoretical. Recovered starting material weighed about 3 grams.

Anal. Calcd. for $C_{16}H_{14}O_2S$: N.E., 270.2; S, 11.9. Found: N.E., 270; S, 11.4.

Cyclization of γ-2-Dibenzothienylbutyric acid.

Four grams of dibenzothienylbutyric acid was dissolved in 100 cc. of 88 per cent sulfuric acid and stirred for 15 minutes at room temperature. The deep red solution was then poured over ice and, after standing, the dilute acid was decanted from the green, tarry precipitate. The precipitate was washed with dilute sodium hydroxide, filtered, and dried. Weight, 1.5 g. By dissolving in hot alcohol and treating with norite, silvery leaves of 1-keto-1,2,3,4-tetrahydrothiobrazan, m.p. 175.5-176.5° were obtained. Further recrystallization raised the melting point to 178°.

Anal. Calcd. for $C_{16}H_{12}OS$: S, 12.7. Found: S, 12.6.

Preparation of o-2-Dibenzothenoylbenzoic Acid.

In a 4-L. flask was placed a mixture of 92 g. (0.5 mole) of dibenzothiophene and 82 g. (0.55 mole) of phthalic anhydride in 500 cc. of a 2:1 mixture of tetrachloroethane and nitrobenzene. The flask was immersed in an ice bath and, with stirring, 100 g. of powdered anhydrous aluminum chloride was added over a period of two hours. Stirring was continued for 10 hours and the reaction flask was then well packed in ice and left over night. In the morning the mixture was again thoroughly cooled and hydrolyzed with 250 g. of ice and 150 cc. of hydrochloric acid at as low a temperature as possible (0-25°). Most of the mixed solvent was then steam distilled off and the reaction mixture allowed to cool. The water layer was then decanted from the cake and the cake washed with water and finally treated with a solution of 100 g. of sodium carbonate in 750 cc. of water. Steam distillation was then continued until very little more solvent would distil and the rest was then removed by ether extraction of the cooled sodium carbonate solution. Acidification with hydrochloric acid precipitated 135 g. of crude acid, melting, with considerable frothing, at 120-125°. This material is doubtless an unstable hydrate of the desired product and no attempt was made to purify it for analysis. Instead, the ethyl ester was made and analyzed (see below).

Preparation of Ethyl o-2-Dibenzothenoylbenzoate.

A gram of the powdered benzoic acid derivative was treated in ether suspension with excess diazoethane. After standing for about 5 hours in the refrigerator, the ether solution was evaporated to dryness. The resulting oil was washed with sodium carbonate solution and recrystallized by treating with petroleum ether (b.p. 60-68°). The colorless, crystalline product melted at 105-106°.

Anal. Calcd. for $C_{22}H_{16}O_3S$: S, 8.91. Found: S, 9.04.

Cyclization of o-2-Dibenzothenoylbenzoic Acid.

The method of cyclization is one used by Fieser and Fieser[44]. A mixture of 4.16 g. of sodium chloride and 20.83 g. of anhydrous aluminum chloride was fused over a free flame and, while at 100-110°, 3 g. of o-2-dibenzothenoylbenzoic acid was added with stirring. The mixture was kept at 150° for thirty minutes with constant stirring and then was poured onto ice. Digestion of the resulting fine emulsion near the boiling point caused coagulation and easy filtration. Yield of crude, dark green solid, 2.6 g., insoluble in sodium carbonate solution. The crude product was extracted with boiling benzene, which was filtered hot. Evaporation of the benzene left a yellow product which, after several recrystallizations from glacial acetic acid melted at 285-286°.

Anal. Calcd. for $C_{20}H_{10}O_2S$: S, 10.2. Found: S, 10.2.

Sulfonation of p-Xenylamine.

The same procedure was followed as given by Courtot and Evain[56] for the preparation of benzidine sulfone. In a 250-cc. three-necked flask was placed 150 cc. of fuming (20 per cent) sulfuric acid. With stirring, 20 g. of p-xenylamine was slowly added, causing the temperature to rise to 70°. The mixture was then stirred at 80° for five hours, after which it was cooled and poured over cracked ice. The only product which was obtained was an acidic material which answered the description of the sulfonic acid obtained by Carnelley and Schlesselman[46].

Preparation of 1,4-Dihydrodibenzothiophene.

About 600 cc. of liquid ammonia was put in a 1-L. three-necked flask and in it was dissolved 10 g. (about 40 per cent excess) of sodium. Slowly, and with stirring, 30 g. (0.16 mole) of dibenzothiophene was added. The

(56) Courtot and Evain, Bull. soc. chim., (4) 49, 527 (1931).

mixture was stirred an additional 40 minutes with the addition, from time to time, of more liquid ammonia as required. The excess sodium and reaction products were then ammonolyzed by the cautious addition of 50 g. of solid ammonium nitrate. When the ammonia had all evaporated, the solid residue was separated into its ether- and water-soluble parts and the ether solution was dried over calcium chloride. The ether solution was then freed of solvent and the product distilled under reduced pressure. The crude product, weighing 26 g. and representing an 85 per cent yield, was collected at 160-165°/6 mm. Losses upon recrystallization are large, but after recrystallization from methanol the melting point was 76°.

Anal. Calcd. for $C_{12}H_{10}S$: C, 77.36; H, 5.42. Found: C, 77.44; H, 5.50.

Picrate of 1,4-Dihydrodibenzothiophene.

One gram (0.0054 mole) of dihydrodibenzothiophene was dissolved in 15 cc. of hot alcohol and treated with a hot solution of 1.4 g. (0.006 mole) of picric acid in 11 cc. of alcohol. The solution became red and, upon cooling, deposited 1.3 g. of beautiful red needles. Melting point after one recrystallization from alcohol, 105°. Treatment with aqueous ammonia regenerated the dihydrodibenzothiophene.

Reaction of 1,4-Dihydrodibenzothiophene with Bromine.

One-half gram of dihydrodibenzothiophene dissolved in 10 cc. of chloroform was cooled in an ice bath and cautiously treated with a carbon tetrachloride solution of bromine until the faint color of bromine persisted. Nearly the theoretical amount of bromine was absorbed and no hydrogen bromide was evolved (ammonia test). In one experiment, when the solvents were removed under diminished pressure and the residue recrystallized from methanol, nearly a quantitative yield of dibenzothiophene (mixed melting point) was obtained. In another experiment the solvents were carefully removed and the oil remaining was kept cool for a long period of time without crystallizing. Evidently the bromine addition product is unstable and loses hydrogen bromide easily, as in the case of dihydronaphthalene[57].

Reaction of 1,4-Dihydrodibenzothiophene with Phenyllithium.

Phenyllithium was prepared in the usual manner from 23.6 g. (0.15 mole) of bromobenzene and 2.1 g. (0.30 g.-atom) of lithium. The resulting solution of phenyllithium in 75 cc. of ether was strained into a flask containing 10 g. (0.054 mole) of dihydrodibenzothiophene dissolved in 75 cc. of ether. The mixture was kept at 0° under nitrogen and immediately became red in color, becoming darker during the first hour. After two hours a fine precipitate was visible and after three hours the ice bath was removed and the mixture allowed to come to room temperature and remain there for an hour. It was then heated to reflux gently for four hours, cooled, and carbonated. Before carbonation the mixture had a pink appearance on account of the heavy white precipitate suspended in it. The mixture remaining after removal of the carbon dioxide was extracted with dilute sodium hydroxide solution. From the water layer was obtained 5 g. of benzoic acid after purification, and no trace of the sparingly soluble dibenzothiophenecarboxylic acids. Distillation of the ether layer, after drying, gave a gram of benzene which was identified through its dinitro derivative. Probably more benzene was present, judging from the odor and the behavior of the remaining mass upon

(57) Bamberger and Lodter, Ber., 20, 1706 (1887).

attempts to sublime it. The solid material left was distilled under diminished pressure to give 9 g. of solid melting at 92-94°, which, when recrystallized from alcohol, was identified as dibenzothiophene (mixed melting point).

Reaction of 1,4-Dihydrodibenzothiophene with Phenylisopropylpotassium.

Phenylmagnesium bromide was prepared from 27 g. (1.1 g.-atom) of magnesium, 181 g. (1.15 mole) of bromobenzene, and 450 cc. of ether according to directions in "Organic Syntheses"[58]. To the solution of Grignard reagent was added an excess of dry acetone. Hydrolysis of the product was effected by a cold aqueous solution of ammonium chloride. Distillation of the crude, dried product gave 113 g. of water-clear α,α-dimethylbenzyl alcohol, b.p. 93-97°/15-20 mm.

The carbinol was converted to the corresponding chloride and then to 2-phenylisopropyl methyl ether according to the directions of Klages[59], as modified by Ziegler and co-workers[60].

Phenylisopropylpotassium was prepared by adding 5 cc. of sodium-potassium alloy (1:5) to a solution of 5.25 g. (0.035 mole) of 2-phenylisopropyl methyl ether in 175 cc. of anhydrous diethyl ether. The reaction started at once and was judged complete after stirring the mixture for 16 hours at room temperature.

The deep-red solution was then transferred to another flask containing 3 g. (0.016 mole) of 1,4-dihydrodibenzothiophene. This mixture was then refluxed for 7 hours, carbonated, and worked up in the usual manner. From

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(58) Gilman, "Organic Syntheses, Collective Volume I", John Wiley and Sons, New York (1932), p. 221.
(59) Klages, Ber., 35, 2638 (1902).
(60) Ziegler and co-workers, Ann., 473, 18-21 (1929).

the ether layer was obtained one gram of dibenzothiophene, identified by the method of mixed melting point. From the water layer there was obtained 2.8 g. of a crude acidic material which could not be recrystallized to a constant melting point. It appears quite probable that dehydrogenation of the dihydrodibenzothiophene occurred first, to be followed by metalation of the resulting dibenzothiophene by the excess organometallic compound present. On account of the high activity of the organopotassium compounds, it might be assumed that mono- and polymetalation occurred, giving a mixture of difficultly separable acids.

Hydrogenolysis of Phenyllithium.

Phenyllithium was prepared in the conventional apparatus from 23.6 g. (0.15 mole) of bromobenzene, 2.1 g. (0.30 g.-atom) of finely cut lithium, and 75 cc. of ether. It was then filtered into the bottle of a hydrogenation apparatus, under protection of nitrogen, and the ether evaporated off. Then about 50 cc. of redistilled petroleum ether, b.p. 115-130°, was added to the bottle and the mixture subjected to a hydrogen pressure of 100 lb. (gauge) with shaking for about 70 hours, when the absence of a color test showed reduction to be complete. The bottle was then removed from the shaker and the mixture carbonated with solid carbon dioxide, and worked up by adding ether and water (cautiously) and separating in the usual manner. From the ether layer, by distillation through a Widmer column, was isolated in a single fractionation, about 4 g. of benzene. From the water layer no benzoic acid could be obtained. In another similar experiment, before any water was added after carbonation, some of the white, powdered solid under the petroleum ether was carefully removed and placed in the flask of a Kohler Grignard machine under dry dioxane. Water was then carefully added and the gas evolved measured and the alkali subsequently titrated. One measurement gave 0.00072 moles of hydrogen and required 0.00078 equivalents of standard acid. A second determination gave 0.00027 moles of hydrogen and required 0.00024 equivalents of acid. This was taken as evidence that the white solid from the hydrogenolysis is lithium hydride. The gas evolved was explosive, when mixed with air, and behaved like hydrogen.

SUMMARY

The chemistry of furan analogs has been extended in the foregoing work on the sulfur analog, dibenzothiophene. A review of the natural occurrence and methods of preparation of dibenzothiophene, and of several general methods for the ring closure synthesis of dibenzothiophene derivatives has been made.

The orientation of the dibenzothiophene nucleus in nitration, halogenation, and sulfonation has been discussed, and it has been shown that acetylation affects the same position.

Dibenzothiophene has been found to undergo metalation by several organolithium compounds in the 4-position, by phenylcalcium iodide in a different position, probably position 3, and by mercuric acetate in an unestablished position. By metalation with n-butyllithium the carboxylic acid and the methyl and hydroxy derivatives have been prepared. From the latter the corresponding methoxy and amino compounds have been synthesized.

Some polycyclic compounds obtained through the Friedel-Crafts reaction of dibenzothiophene and acid anhydrides, followed by cyclization, have been described.

The preparation of 1,4-dihydrodibenzothiophene and its reactions with bromine and some organometallic compounds have been reported. In this connection the hydrogenolysis of phenyllithium has also been discussed.