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CHEMICAL INVESTIGATIONS OF FLUORINE COMPOUNDS AS FUNGICIDES

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DIVISION OF FLUORINE CHEMISTRY
ILLINOIS STATE GEOLOGICAL SURVEY

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WRIGHT AIR DEVELOPMENT CENTER

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FOREWORD

This report was prepared by the Illinois State Geological Survey, under USAF Contract No. AF 33(038)-26990. The contract was initiated under Research and Development Order No. 611-15, "Preservative Chemicals", and was administered under the direction of the Materials Laboratory, Directorate of Research, Wright Air Development Center, with Dr. Alton E. Prince acting as project engineer.

ABSTRACT

Fifteen aromatic fluorine compounds were prepared for fungicidal screening tests since 1 September 1952. The syntheses and properties of these compounds and intermediates are described in detail except in cases of known or borrowed derivatives. Ten of the test samples are new to the scientific literature. Classes represented are fluorinated benzoic acids, phenols, anisoles, toluenes, biphenols, biphenyl sulfide, and benzyl derivatives.

A search was made for colorless and thermally stable fungicides in the biphenyl and biphenyl sulfide classes. Three solid fluorinated hydroxybiphenyls, also called biphenols, were synthesized with 2,2'-dihydroxy-5,5-difluorobiphenyl showing the most promise. When a sulfur linkage was introduced into the latter to give a biphenyl sulfide, fungicidal potency was increased so that 24-95 parts per million prevented growth of four test fungi.

Cotton thread impregnated with the sulfur compound showed no discoloration or loss in tensile strength, and when treated with 1000 ppm solution was completely protected. Likewise, 2-fluoro-6-nitrophenol, a potent fungicide, and the difluorobiphenols did not appear to change the tensile strength of the thread.

Twelve compounds were prepared on a fairly large laboratory scale for the Materials Laboratory for evaluation studies. A total of 1900 g. of material packaged as 100-200-g. samples were delivered for this purpose.

PUBLICATION REVIEW

This report has been reviewed and is approved.

FOR THE COMMANDER:

M. R. WHITMORE
Technical Director
Materials Laboratory
Directorate of Research

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INTRODUCTION

The synthesis of some fluorinated quinones by Finger et al[1] in 1949 at the Illinois State Geological Survey led to the discovery of their fungicidal properties by Tehon[2] of the Illinois State Natural History Survey. Air Force materiel protection scientists, desiring to include organic fluorides in their search for new fungicides, initiated a fungicidal screening program with Dr. L. R. Tehon in March 1950, and a chemical research program with the Geological Survey in July 1951.

Thirty-five compounds were covered in the first chemical report[3], of which the nitrophenol and dinitro types showed the most promise. The most sensational discovery was 1-fluoro-3-bromo-4,6-dinitrobenzene which inhibits the growth of A. niger at 0.8 parts per million.

This final chemical research report covers the period from 1 September 1952 to the end of the contract, 30 April 1954. Fifteen compounds were synthesized for the screening program, and some large-scale laboratory preparations were studied.

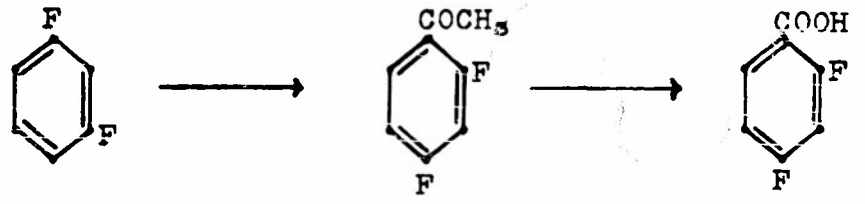
Complete information on the fungicidal investigation program is found in the Tehon reports[4], and any fungicidal data appearing in the chemical studies come from this source.

SECTION I

FLUORINE COMPOUNDS STUDIED#

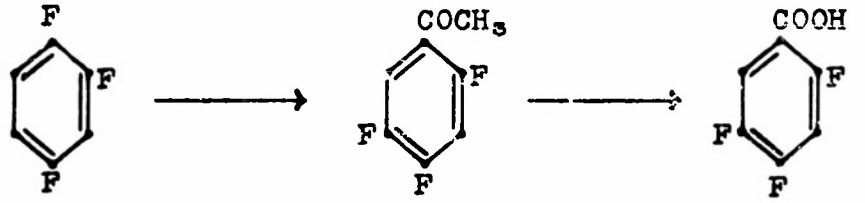
A. Benzoic Acids

Two fluorinated benzoic acids were prepared, namely the 2,4-difluoro and 2,4,5-trifluoro compounds. They were conveniently obtained by oxidation of the appropriate fluoroacetophenones.



I III

2,4-Difluorobenzoic Acid, M.p. 183-184°



II IV

2,4,5-Trifluorobenzoic Acid M.p. 97-98°

These acids are white solids, slightly water soluble, soluble in alkali, acetone, alcohol, insoluble in petroleum ether, and sublime upon heating.

It is known that monofluorobenzoic and the chlorobenzoic acids have mild astringent and antiseptic properties; thus it was

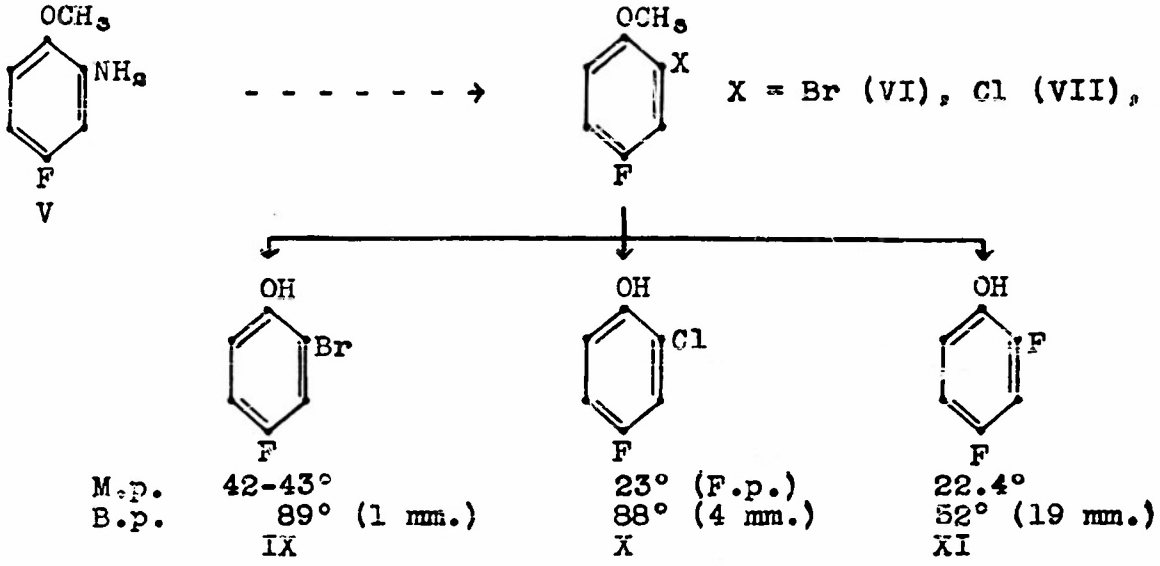
#Temperature reported in °C.

thought that polyfluorobenzoic acids may exhibit similar properties. Complete growth inhibition of A. niger and C. globosum for the difluoro acid occurred at about 350 and 525 ppm, respectively, whereas the trifluoro acid was 480 and 700 ppm. These potencies are not outstanding, and it might also be concluded that increased fluorine content is of very little significance.

B. Phenols and Nitrophenols

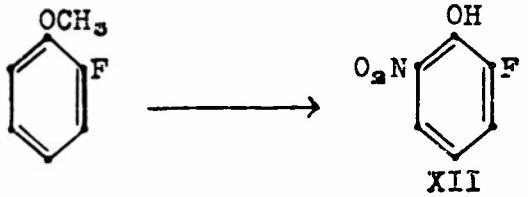
Five phenols were studied, three of the 2-halo-4-fluoro, and two of the fluoronitro types.

The 2-halo-4-fluoro types were studied because 2,4-dihalophenols[5] are reported to have better phenol coefficients than the monohalophenols, and dissimilar halogens increase fungicidal potency in dihalodinitrobenzenes[3,4]. With the synthesis of a key intermediate, 2-amino-4-fluoroanisole (V), other research made available 2-bromo-4-fluorophenol (IX) and 2-chloro-4-fluorophenol (X) as new compounds, and 2,4-difluorophenol (XI). The scheme of synthesis and pertinent physical data are given. The bromo compound may be obtained more conveniently by bromination of 4-fluorophenol in aqueous solution with a near 80% yield.

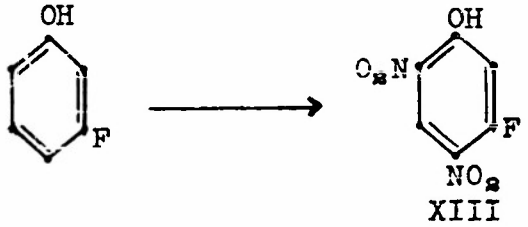


Growth inhibition for A. niger in parts per million was about 140 of Br-F, 400 of Cl-F, and 400 of F-F as compared to 600 for 4-fluorophenol. This shows some advantage in multiple and dissimilar halogens.

The nitrophenols studied since the last report[3] are indicated in the scheme of preparation, and both are known



2-Fluoro-6-nitrophenol
M.p. 91-92°



3-Fluoro-4,6-dinitrophenol
M.p. 79-80°

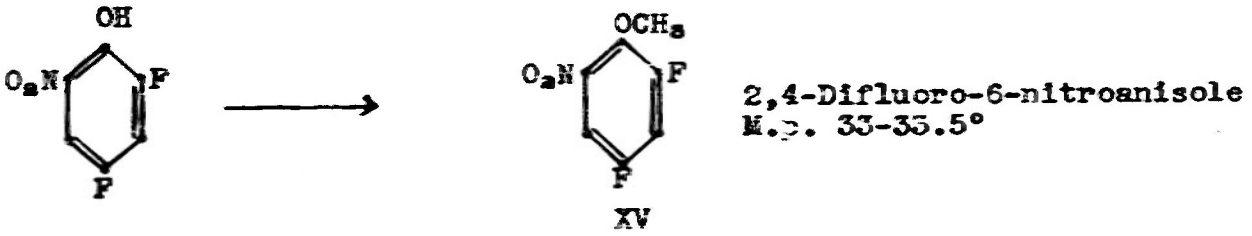
compounds. They are yellow solids, quite insoluble in water but soluble in alkali, and are readily soluble in the usual organic solvents.

Growth inhibition for A. niger was 11.5 ppm for XII and 130 ppm for XIII, thus reaffirming previous observations of potency exaltation of nitro groups. On the other hand, 2-nitro-4-chlorophenol at 10-30 ppm[4] is also quite effective as a fungicide.

Cotton parachute webbing impregnated with XII showed a yellow color and no apparent change in tensile strength.[4]

C. Nitroanisoles

Conversion of a phenol to an anisole or methyl ether derivative causes a decided decrease in fungicidal potency. This was again clearly demonstrated with 2,4-difluoro-6-nitrophenol[3] when it was converted to the anisole (XV). The phenol prevents A. niger growth at 50 ppm, whereas the anisole permits some growth at 600 ppm.



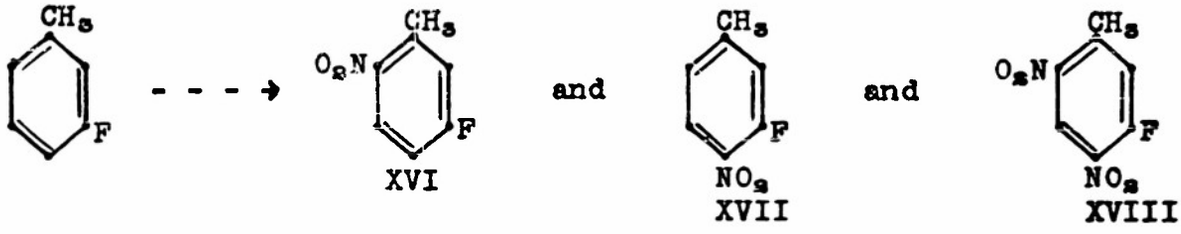
2,4-Difluoro-6-nitroanisole
M.p. 33-35.5°

XV

Preparation of the nitroanisole was readily accomplished by the nitration of 2,4-difluoroanisole in a 44% yield.

D. Nitrotoluenes

Since 3-fluoro-4,6-dinitrotoluene (XVIII)[3,4] shows excellent fungicidal properties, it appeared worth-while to study the potency of two isomeric precursors, 3-fluoro-4-nitrotoluene (XVII) and 3-fluoro-6-nitrotoluene (XVI). These compounds are available from the nitration of 3-fluorotoluene and it is interesting to note that both mononitro compounds will yield the same dinitro derivative. They are yellow solids except the dinitro compound is almost colorless.



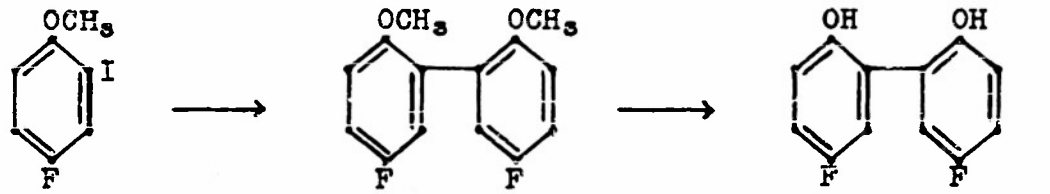
	XVI	XVII	XVIII
M.p.	27-28°	53°	78-79°
Potency (ppm)	1000	400	3.9

The concentrations required to inhibit growth of A. niger are indicated below the formulae in parts per million as potency.

E. Biphenols

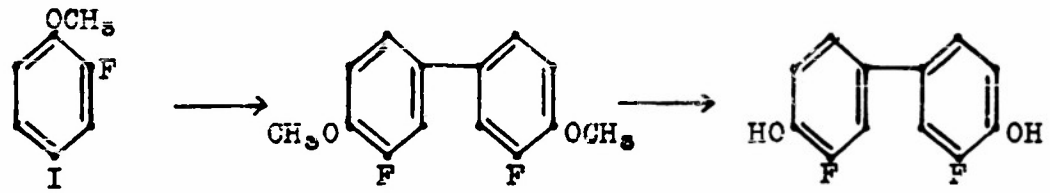
The biphenols or hydroxybiphenyls and their chlorinated derivatives are known to have bactericidal properties[5], and some of these compounds are available under various trade names. Since fluorinated biphenols had not been investigated as possible fungicides, and since it was possible that they may be colorless, heat-stable compounds suitable for incorporation into plastics, some preliminary studies were undertaken.

Three fluorinated biphenols were prepared - 2,2'-dihydroxy-5,5'-difluorobiphenyl (XXI), 3,3'-difluoro-4,4'-dihydroxybiphenyl (XXIV) and 2,2'-dihydroxy-3,3',5,5'-tetrafluorobiphenyl (XXVII). The scheme of synthesis involved an Ullmann[6] coupling reaction on the appropriate iodofluoroanisoles to the bianisoles followed by an aluminum chloride ether cleavage to the biphenols.



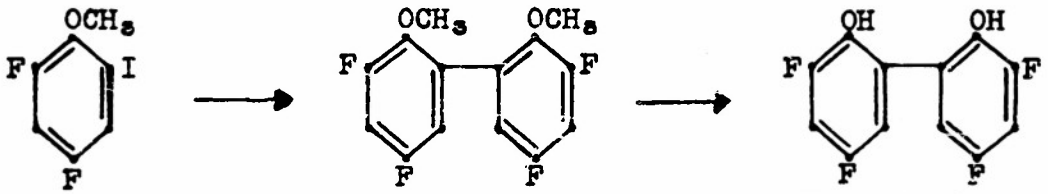
XIX XX XXI

M.p. 138-139°



XXII XXIII XXIV

M.p. 189°



XXV XXVI XXVII

M.p. 173°

These compounds are odorless, white solids, fairly high melting, slightly soluble in hot water and petroleum ether,

moderately soluble in ethanol, and soluble in alkali.

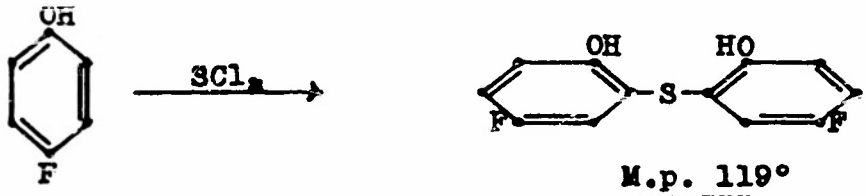
Growth inhibition of A. niger was obtained at 140, 200 and 230 ppm for XXI, XXIV, and XXVII, respectively. These biphenols are more potent than the simple fluorophenols, XXI shows the most promise and on the basis of the tetrafluoro (XXVII) compound multiple fluorine substitution is of no advantage.

Impregnation of cotton thread by the difluorobiphenols did not appear to affect the tensile strength[4].

F. Biphenyl Sulfide

Sulfur and a number of its compounds are among the oldest industrial fungicides known. Within recent years a great deal of attention is being directed to organic sulfur compounds[7] such as dithiocarbamates, thiuram disulfides, mercaptobenzothiazoles and others. It is interesting to note that 2,2'-dihydroxy-3,3',5,5'-tetrachlorobiphenyl sulfide[8], known in the trade as Actamer (Monsanto) and Lorothiodol (Hilton Davis Chemical Co.), are reported as having bactericidal and fungicidal properties.

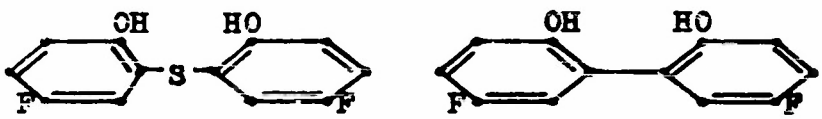
In view of the fungicidal activity of the fluorinated biphenols, it was speculated that a sulfur linkage between the phenyl groups would give increased potency. For a test case, 2,2'-dihydroxy-5,5'-difluorobiphenyl sulfide (XXVIII) was synthesized from 4-fluorophenol and sulfur dichloride. The compound is a white solid with a mild cresol-like odor, soluble in the



M.p. 119°
XXVIII

usual organic solvents and alkali, insoluble in water, and fairly soluble in high boiling petroleum ether.

Fungicidal potency[4] was increased by the introduction of the sulfur linkage as indicated in the concentrations required to stop growth of four test fungi.



C. globosum	24 ppm	37 ppm
M. verrucaria	26.5 "	110 "
A. terreus	72 "	80 "
A. niger	95 "	140 "

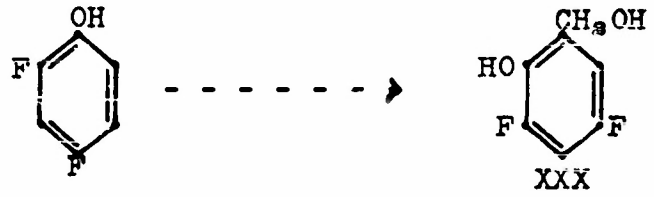
Cotton thread impregnated with the sulfur compound showed no discoloration or loss in tensile strength, and when treated with a 1000 ppm solution was completely protected against fungus damage[4].

G. Benzyl Derivatives

A sample of 2,4,6-trifluorobenzyl chloride[9] (XXIX) possessed only very mild fungistatic potency.

The introduction of a $-CH_2OH$ group in the aromatic nucleus increases solubility, and in the form of salicyl alcohol (saligenin)

a mild antiseptic is obtained. It was speculated that perhaps a fluorinated salicyl alcohol may offer some possibilities as a fungicide. This compound at 600 ppm showed only 25% reduced growth



XXX M.p. 61-63°

2-Hydroxy-3,5-difluorobenzyl alcohol

of A. niger, but complete inhibition of C. globosum. It is interesting to note that the parent compound is a better fungicide than the benzyl derivative.

SECTION II

EXPERIMENTAL PROCEDURES

2,4-Difluoroacetophenone (I).--The usual Friedel-Crafts acylation procedure was modified in that an excess of the aryl halide was used to serve both as a reactant and solvent.

To a well-stirred mixture of 114 g. of 1,3-difluorobenzene[10] and 80 g. anhydrous aluminum chloride, 48 cc. of acetic anhydride was added slowly and the resulting mixture refluxed for one hour. After pouring over ice, steam distillation removed the acetophenone and the unreacted difluorobenzene. A yield of 32 g. (41%) of crude difluoroacetophenone was obtained and a vacuum distillation gave pure 2,4-difluoroacetophenone, f.p. ca. +9°, b.p. 89°, n_D^{20} 1.4881.

Anal. Calcd. for $C_8H_6F_2O$: C, 61.54; H, 3.87; F, 24.34. Found: C, 61.47; H, 3.76; F, 24.47.

2,4,5-Trifluoroacetophenone (II).--This compound was obtained by the above procedure, except that 1,2,4-trifluorobenzene[11] was the aryl halide.

The yield of the acetophenone was 45%. A vacuum distillation gave pure 2,4,5-trifluoroacetophenone, f.p. ca. 7°, b.p. 99-101° (20 mm.), n_D^{20} 1.4718.

Anal. Calcd. for $C_8H_5F_3O$: C, 55.18; H, 2.89; F, 32.74. Found: C, 55.12; H, 2.94; F, 32.58.

2,4-Difluorobenzoic Acid (III).--A mixture of 4.3 g. of 2,4-difluoroacetophenone, 8 g. of potassium permanganate, 160 ml. water, 3 ml. of 10% sodium hydroxide solution was refluxed 5 hours. More permanganate solution was added during the refluxing to complete the oxidation. After removal of the manganese dioxide by filtration, acidification of the filtrate gave the crude difluorobenzoic acid as a white precipitate, yield 3.7 g. (85%). Recrystallization from water followed by sublimation gave pure 2,4-difluorobenzoic acid, m.p. 183-184°. It is interesting to note that a mixed melting point (181-182°) with 4-fluorobenzoic acid (m.p. 182-184°) shows no significant depression.

Anal. Calcd. for $C_7H_4F_2O_2$: C, 53.18; H, 2.55; F, 24.04. Found: C, 53.32; H, 2.44; F, 24.01.

2,4,5-Trifluorobenzoic Acid (IV).--This acid was prepared from 2,4,5-trifluoroacetophenone by the oxidation procedure previously described.

Recrystallization of the crude acid from carbon tetrachloride followed by sublimation gave pure 2,4,5-trifluorobenzoic acid, m.p. 97-98°.

Anal. Calcd. for $C_7H_3F_3O_2$: C, 47.74; H, 1.72. Found: C, 47.77; H, 1.67.

2-Amino-4-fluoroanisole (V).--To a mixture of 123 g. of iron filings and one liter of ammonium chloride solution (0.78 N) with stirring, 122.5 g. of liquified 2-nitro-4-fluoroanisole[12] was added slowly. After completion of the reduction, the amine was removed by steam distillation as a heavy oil. Crude yield was 92 g. Vacuum distillation gave pure 2-amino-4-fluoroanisole, f.p. ca. 3°, b.p. 117° (20 mm.).

Anal. Calcd. for C_7H_8FNO: C, 59.56; H, 5.71; N, 9.92. Found: C, 59.55; H, 5.53; N, 9.84.

The acetyl derivative after recrystallization from ethanol followed by sublimation was obtained as white plates, m.p. 101-102°.

Anal. Calcd. for $C_9H_{10}FNO_2$: N, 7.65. Found: N, 7.60.

2-Bromo-4-fluoroanisole (VI).--A Sandmeyer-cuprous bromide reaction on 2-amino-4-fluoroanisole (V) gave an 89% yield of steam-distilled crude product. Vacuum distillation gave pure 2-bromo-4-fluoroanisole, f.p. ca. -27°, b.p. 79° (5 mm.), n_D^{20} 1.5447.

Anal. Calcd. for C_7H_6BrFO: C, 41.00; H, 2.95; Br, 38.98; F, 9.27. Found: C, 41.19; H, 2.83; Br, 39.29; F, 9.07.

2-Chloro-4-fluoroanisole (VII).--This compound was obtained from V by a Sandmeyer-cuprous chloride synthesis in an 88% crude yield.

The pure compound is a heavy colorless oil, b.p. ca. -17°, b.p. 67° (5 mm.), n_D^{20} 1.5173.

Anal. Calcd. for C_7H_6ClFO: C, 52.35; H, 3.77; Cl, 22.08; F, 11.83. Found: C, 52.55; H, 3.75; Cl, 21.87; F, 12.12.

2,4-Difluoroanisole (VIII).--Schiemann[13] reported the synthesis of this compound from 2-fluoro-4-aminoanisole.

For this study it was prepared from V by the Schiemann transformation[14] in an overall yield of about 50%. Data on the pure compound are f.p. -15.5°, b.p. 151°, n_D^{20} 1.4705.

2-Bromo-4-fluorophenol (IX).--This compound was borrowed initially from other research and had been obtained from VI by ether cleavage[15] reactions. A more convenient method is the direct bromination of 4-fluorophenol.

To a well-stirred suspension of 112 g. of 4-fluorophenol[16] in 500 ml. of water at 20°, 160 g. of liquid bromine was added dropwise over a period of two hours. The heavy oil layer was treated with dilute sodium carbonate solution to alkalinity, and steam distilled. After separation and drying of the oily distillate,

vacuum distillation gave a main fraction, b.p. 90° (2.5 mm.), which solidified on cooling to pale yellow needles, m.p. 40-42°, yield 151 g. or 79%. The melting point of an analytically pure sample is 42-43°.

2-Chloro-4-fluorophenol (X)[15].--This is a new compound, f.p. ca. 23°, b.p. 88° (4 mm.), and was loaned to this project.

2,4-Difluorophenol (XI).--The procedure used by Schiemann[13] for preparing this compound was used. An aluminum chloride ether cleavage of VIII gave an 84% yield of the crude phenol. Data on the pure compound are m.p. 22.4°, b.p. 52° (19 mm.) or 74° (50 mm.).

2-Fluoro-6-nitrophenol (XII).--This compound was prepared from 2-fluoroanisole[17] as described in the literature by Niemann et al[18]. The pure material, which was obtained by recrystallization from aqueous ethanol, formed yellow needles, m.p. 91-92°, yield 44%.

3-Fluoro-4,6-dinitrophenol (XIII).--Hodgson[19] obtained this compound by the nitration of 3-fluorophenol, and recrystallization from aqueous ethanol gave a white solid, m.p. 79-80°.

2,4-Difluoro-6-nitroanisole (XV).--This compound had been prepared previously by the methylation of 2,4-difluoro-6-nitrophenol[20] in another study[9]. An improved method described

below was developed involving the direct nitration of 2,4-difluoroanisole.

To a solution of 75 g. (0.5 mole) of 2,4-difluoroanisole[13] in 80 ml. of acetic anhydride with stirring, a mixture of 47 g. (0.75 mole) of 100% nitric and 42 ml. of acetic acids was added slowly in 50 minutes, and the reaction temperature controlled at 35-40°with a water bath. Stirring was continued for six hours at 38-45°. After pouring over ice, the crude nitro layer was made alkaline with sodium carbonate solution, and steam distilled. The dried, steam distilled product on vacuum fractionation gave 41 g. or 44% yield of pure 2,4-difluoro-6-nitroanisole, b.p. 66-67° (3 mm.). A small amount of an unidentified by-product was obtained.

3-Fluoro-(6 or 4)-nitrotoluene (XVI and XVII).--These compounds were obtained by Schiemann[21] by the nitration of 3-fluorotoluene with fuming nitric acid. The 6-nitro compound is obtained in the largest amount. Melting points of XVI and XVII are 27-28° and 53°, respectively.

3-Fluoro-4,6-dinitrotoluene (XVIII).--This compound was reported[3] previously and was obtained in a 95% yield by a mixed acid nitration of 3-fluorotoluene[21], m.p. 78-79°.

2-Iodo-4-fluoroanisole (XXIX).--This compound was prepared from 2-amino-4-fluoroanisole (V) in a 78% yield of crude

steam distilled product by the usual Sandmeyer reaction. Vacuum distillation gave pure 2-iodo-4-fluoroanisole, f.p. ca. -21°, b.p. 92° (3 mm.), n_D^{20} 1.5924.

Anal. Calcd. for C_7H_6FIO: C, 33.36; H, 2.40; F, 7.54; I, 50.36. Found: C, 33.41; H, 2.41; F, 7.68; I, 50.69.

2,2'-Dimethoxy-5,5'-fluorobiphenyl (XX).--An Ullmann coupling reaction[6] was performed on the preceding anisole to give the desired bianisole.

The general procedure for the Ullmann coupling reaction was to heat by an oil bath equal weights of the iodofluoroanisole and copper bronze in a large test tube equipped with an air condenser. Reaction temperatures and heating time varied with the compound in question, and occasionally more copper was added during the reaction period. Extraction of the reaction mass in a Soxhlet with acetone removed the crude biphenyl.

A 70% crude yield was obtained from the coupling of 2-iodo-4-fluoroanisole at 190-210° for 2 1/2 hours. Recrystallization from ethanol gave white needles, m.p. 121-121.5°.

Anal. Calcd. for $C_{14}H_{12}F_2O_2$: C, 67.19; H, 4.84; F, 15.19. Found: C, 67.25; H, 4.63; F, 14.97.

2,2'-Dihydroxy-5,5'-difluorobiphenyl (XXI).--This compound was prepared by an aluminum chloride split[22] of the corresponding ether.

A mixture of 9.3 g. of 2,2'-dimethoxy-5,5'-difluorobiphenyl, 30 g. of anhydrous aluminum chloride and 80 ml. of benzene was refluxed overnight. The reaction mixture was poured over ice, steam was blown through the mixture to remove the benzene, and after the residue had cooled, the crude product was recovered by filtration. Dilute sodium hydroxide solution was added to the crude material and the resulting mixture extracted with ether. Acidification of the alkaline extract reprecipitated the biphenol, yield 6.3 g. (76%). Recrystallization from ethylene dichloride gave pure 2,2'-dihydroxy-5,5'-difluorobiphenyl as hard, white crystals, m.p. 138-139°.

Anal. Calcd. for $C_{12}H_8F_2O_2$: C, 64.87; H, 3.63; F, 17.10. Found: C, 65.06; H, 3.35; F, 17.38.

2-Fluoro-4-iodoanisole (XXII).--An 83% crude yield of this compound was obtained from 2-fluoro-4-aminoanisole[23] by a Sandmeyer reaction. Recrystallization from ethanol followed by vacuum sublimation gave the pure compound, m.p. 33.5-34°.

Anal. Calcd. for C_7H_6FIO: C, 33.36; H, 2.40; F, 7.54; I, 50.36. Found: C, 33.48; H, 2.30; F, 6.87, 7.40; I, 51.51, 51.01.

3,3'-Difluoro-4,4'-dimethoxybiphenyl (XXIII).--By the general procedure under XX, the preceding anisole was coupled by heating at 190-210° for about four hours, and a 70% yield of crude biphenyl was obtained. A recrystallization from a benzene-ethanol mixture gave the pure biphenyl as white platelets, m.p. 153-154°.

Anal. Calcd. for $C_{14}H_{12}F_2O_2$: C, 67.19; H, 4.84; F, 15.19. Found: C, 67.08; H, 4.63; F, 15.00.

3,3'-Difluoro-4,4'-dihydroxybiphenyl (XXIV).--By the procedure indicated under XXI, 3,3'-difluoro-4,4'-dimethoxybiphenyl was split with aluminum chloride to the corresponding biphenol in a 92% crude yield. The crude product was recrystallized from an ethanol-ethylene dichloride mixture to the pure biphenol, m.p. 188.5-189°.

Anal. Calcd. for $C_{12}H_8F_2O_2$: C, 64.87; H, 3.63; F, 17.10. Found: C, 64.92; H, 3.62; F, 17.04.

2-Iodo-4,6-difluoroanisole (XXV).--An amine hydrosulfate slurry was prepared by the slow addition of 2-amino-4,6-difluoroanisole[9] with stirring to 34 ml. of concentrated sulfuric acid in 150 ml. of water at 60°. Diazotization was effected at 0-5° by adding a solution of 15.2 g. of sodium nitrite in 50 ml. of water, and at the end sulfamic acid was added to destroy excess nitrous acid. The diazonium solution was poured slowly into a stirred solution of 40 g. of potassium iodide in 60 ml. of water, and the temperature held at 5-10° during the evolution of nitrogen. Sodium thiosulfate solution was added to remove the iodine, and the mixture was steam distilled. The crude product, 49 g., was vacuum distilled and a yield of 43 g. or 80% of pure iodo compound was obtained as a heavy oil, b.p. 60-61° (3 mm.), n_D^{20} 1.54933.

Anal. Calcd. for $C_7H_5F_2IO$: C, 31.13; H, 1.87; F, 14.07; I, 47.00. Found: C, 31.31; H, 1.81; F, 14.28; I, 46.72.

2,2'-Dimethoxy-3,3',5,5'-tetrafluorobiphenyl (XXVI).--A mixture of 27 g. of 2-iodo-4,6-difluoroanisole and 35 g. of copper bronze powder was heated at 210° (bath temperature) for three hours. The reaction mass was pulverized, extracted with acetone, and the acetone extract poured into water, whereupon an oil separated and solidified on cooling. Yield of crude product, 12.7 g. or 89%. Recrystallization from aqueous ethanol and a final sublimation gave the pure biphenyl, m.p. 49.5-50°.

Anal. Calcd. for $C_{14}H_{10}F_4O_2$: C, 58.75; H, 3.52; F, 26.55. Found: C, 58.54; H, 3.38; F, 26.35.

2,2'-Dihydroxy-3,3',5,5'-tetrafluorobiphenyl (XXVII).--A mixture of 9 g. of the preceding biphenyl, 26.6 g. of anhydrous aluminum chloride, and 100 ml. of dry benzene was refluxed for five and one-half hours. After pouring the reaction mixture over ice, the benzene was removed by steam distillation, and after chilling the crude solid product was removed by filtration. An ether extraction of the aqueous layer completed the recovery. The crude product was dissolved in 10% sodium hydroxide solution, alkali-insoluble material was removed by ether extraction, and acidification with dilute hydrochloric acid precipitated the crude biphenyl as a white solid, yield 7 g. or 86%. Recrystallization from a

benzene-petroleum ether (low boiling) mixture gave the pure compound as a white powder, m.p. 173°.

Anal. Calcd. for $C_{12}H_6F_4O_2$: C, 55.82; H, 2.34; F, 29.44. Found: C, 55.57; H, 2.20; F, 29.31.

2,2'-Dihydroxy-5,5'-difluorobiphenyl Sulfide (XXVIII).-- This compound is new and was prepared by the Dunning [24] procedure for compounds of this type.

Sulfur dichloride was freshly prepared by passing chlorine into sulfur monochloride at -15° until the theoretical amount of chlorine had been absorbed.

To 124 g. of 4-fluorophenol[17] dissolved in one liter of anhydrous carbon disulfide, 102 g. of freshly prepared sulfur dichloride was added in four hours with stirring at room temperature. Hydrogen chloride gas was evolved. The mixture was heated at refluxing temperature overnight. After pouring over ice, about 68 g. of crude product as an orange precipitate was obtained, and the filtrate gave a dark residue after removal of the carbon disulfide by steam. The residue upon pouring into ice gave 38 g. more of product, thus resulting in a crude yield of 106 g. or 41%. Recrystallization from ethylene dichloride gave white needles, and vacuum sublimation gave the pure compound, m.p. 119°.

Anal. Calcd. for $C_{12}H_6F_2O_2S$: C, 56.68; H, 3.17; F, 14.95; S, 12.61. Found: C, 56.82; H, 3.38; F, 15.10; S. 12.41.

2,4,6-Trifluorobenzyl Chloride (XXIX).--This compound is new and was borrowed from another project[9].

It is a colorless liquid with a slight pungent odor, n_D^{20} 1.47088, b.p. 157°.

2-Hydroxy-3,5-difluorobenzyl Alcohol (XXX).--A mixture of 20 g. of 2,4-difluorophenol[13], 40 ml. of 37% aqueous formaldehyde and 10 ml. of 40% sodium hydroxide solution was refluxed gently for two hours. The reaction mixture was diluted by pouring into 200 ml. of water. With stirring in an ice bath, the diluted mixture was acidified with concentrated hydrochloric acid, and the crude product precipitated as smudgy needles, yield 20.8 g. or 91%. This procedure was adopted from the work of Lederer[25] and Manasse[26,27]. Recrystallization from m-fluorobenzotrifluoride followed by sublimation gave white crystals, m.p. 61-63°.

Anal. Calcd. for $C_7H_6F_2O_2$: C, 52.50; H, 3.78; F, 23.73. Found: C, 52.74; H, 3.60; F, 23.50.

The structure of this compound has not been proved definitely, but all evidence points to the ascribed formula.

SECTION III

SUMMARY

The synthesis and properties of 15 aromatic fluorine compounds prepared for the fungicidal screening program are described. Eight are representatives of types not studied

previously - namely, fluorinated benzoic acids, biphenols, biphenyl sulfides and benzyl derivatives. The remainder may be classified as halogenated phenols, nitrophenols, nitroanisoles, and nitrotoluenes. This brings to about 50 the number of compounds studied in the search for new fungicides applicable to the prevention of mildew or fungus rot damage.

Increased fluorine substitution in the benzoic acids does not bring about any unusual potencies. The benzyl chloride and benzyl alcohol specimens showed up very poorly in the screening tests.

An outstanding case of potency exaltation by a nitro group was discovered with 2-fluoro-6-nitrophenol which arrests the growth of A. niger at 11.5 ppm. The parent, 2-fluorophenol, has very poor fungistatic properties. This may be a unique structural condition as a second nitro group or fluorine atom decreases the potency. With the 2-(F,Cl,Br)-4-fluorophenols, a bromine atom appears to be about three times as effective as fluorine in the 2-position, and thus gives further support to potency boosting by dissimilar halogens.

The potency of 3-fluoro-4,6-dinitrotoluene to A. niger is 250 times the 6-nitro and 100 times the 4-nitro precursors, thus showing the effect of the second nitro group.

Two difluorobiphenols and a tetrafluorobiphenol arrested the growth of A. niger in the range of 140-230 ppm. The tetrafluoro compound showed the lowest potency. A sulfur linkage was

introduced between the phenyl groups of one biphenol, and the growth inhibition concentration range on four test fungi was changed from 37-140 ppm to 24-95 ppm. The biphenols and the biphenyl sulfides may offer some possibilities as colorless, heat-stable fungicides.

Impregnation of cotton parachute webbing thread by 2-fluoro-6-nitrophenol, the difluorobiphenols, and the biphenyl sulfide did not appear to change the tensile strength of the thread.

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APPENDIX I

SUMMARY OF PHYSICAL AND FUNGICIDAL PROPERTIES

(44 Fluorine and 7 non-fluorine compounds)

Name and Appearance of Compound	Compound[a] Empirical Formula	Mol. Wt.	M.p. °C	Concentration as ppm required to prevent growth[b] A. niger	A. terreus	M. verrucaria	C. globosum
PHENOLS							
Phenol White cryst.	C_6H_6O	94	41 (182°)[d]	>800	>800	>800	-
2-Fluorophenol Amber liqd.	C_6H_5FO	112	f.p. 16.1 (151-152)[d]	-	>1500	>1200	1200
3-Fluorophenol Amber liqd.	"	"	f.p. 13.7 (178°)[d]	800	1000	500	500
4-Fluorophenol White cryst.	"	"	48 (185.5°)[d]	600	700	500	>500
2,4-Difluorophenol Colorless liqd.	$C_6H_4F_2O$	130	22.4 (74°/50 mm.)[d]	400	550	400	400
*2-Chloro-4-fluorophenol[c] Colorless liqd.	C_6H_4ClFO	146.5	f.p. 23 (88°/4 mm.)[d]	400	400	350	160
*2-Bromo-4-fluorophenol[c] Yellow cryst.	C_6H_4BrFO	191	42-43 (89°/1 mm.)[d]	140	-	-	210
*2-Methyl-4-fluorophenol Colorless liqd.	C_7H_7FO	126	35 (86°/14 mm.)[d]	300	-	-	-

*New compounds (20 total)

APPENDIX I (cont'd)

Name and Appearance of Compound	Compound[a] Empirical Formula	Mol. Wt.	M.p. °C	Concentration as ppm required to prevent growth[b] A. niger	A. terreus	M. verrucaria	C. globosum
NITROPHENOLS							
2-Nitrophenol Yellow cryst.	$C_6H_5NO_3$	139	45 (214.5)[d]	50 ← ca. 50% reduction in growth →			50
2-Nitro-4-chlorophenol Yellow cryst.	$C_6H_4ClNO_3$	173.5	87	30	-	-	10
2-Nitro-4-fluorophenol Yellow cryst.	$C_6H_4FNO_3$	157	73.7	40	>50	50	40
2-Nitro-6-fluorophenol Yellow cryst.	$C_6H_4FNO_3$	157	91-92	11.5	22.7	9	8.4
*2,4-Difluoro-6-nitrophenol Yellow cryst.	$C_6H_3F_2NO_3$	176	49-50	50	30	40	20
4-Fluoro-2,6-dinitrophenol Yellow cryst.	$C_6H_3FN_2O_5$	202	50	50-55	1000	-	400
3-Fluoro-4,6-dinitrophenol Yellow cryst.	"	"	80	130	180	275	150
Note: Also listed under dinitro compounds.							
NITROANILINES							
2-Nitro-4-fluoroaniline Yellow cryst.	$C_6H_5FN_2O_2$	156	92.5	300	-	-	300
3-Nitro-4-fluoroaniline Yellow cryst.	"	"	98	Active growth at 200 ppm			
2-Nitro-5-fluoroaniline Yellow cryst.	"	"	97	>400	-	150	400
2-Nitro-3,5-difluoroaniline Yellow cryst.	$C_6H_4F_2N_2O_2$	174	107-108	600	-	-	200

APPENDIX I (cont'd)

Compound[a] Name and appearance of compound	Empirical formula	Mol. wt.	M.p. °C	Concentration as ppm required to prevent growth[b] A. niger	A. terreus	M. ver-rucaria	C. globosum
NITROTOLUENES							
2-Nitro-5-fluorotoluene Yellow cryst.	$C_7H_6FNO_2$	155	27-28	1000	-	-	-
3-Fluoro-4-nitrotoluene Yellow cryst.	"	"	53	400	-	-	-
*3-Fluoro-4,6-dinitrotoluene Yellow cryst. Note: Also listed under dinitro compounds	$C_7H_5FN_2O_4$	200	78-79	3.9	7.9	5.5	0.58
DINITRO COMPOUNDS							
1-Chloro-2,4-dinitrobenzene Yellow cryst.	$C_6H_3ClN_2O_4$	202.5	51 (315°)[d]	-	>10	>10	10
1-Fluoro-2,4-dinitrobenzene Yellow liqd. or solid	$C_6H_3FN_2O_4$	186	25.8 (133°/2 mm.)[d]	5	10	2	4
1,3-Dibromo-4,6-dinitrobenzene Yellow cryst.	$C_6H_2Br_2N_2O_4$	326	117	6	-	-	4
1,3-Dichloro-4,6-dinitrobenzene Yellow cryst.	$C_6H_2Cl_2N_2O_4$	237	103	>3	6	1.6	3
1,3-Difluoro-4,6-dinitrobenzene Yellow cryst.	$C_6H_2F_2N_2O_4$	204	75	10-15	10-15	10	ca. 15
1-Fluoro-3-chloro-4,6-dinitrobenzene White cryst.	$C_6H_2ClFN_2O_4$	220.5	76-77	2-3	ca. 3	2.5	2

APPENDIX I (cont'd)

Name and Appearance of Compound	Empirical Formula	Mol. Wt.	M.p. °C	Concentration as ppm required to prevent growth[b] A. niger	A. terreus	M. verrucaria	C. globosum
1-Fluoro-3-bromo-4,6-dinitrobenzene White cryst.	$C_6H_2BrFN_2O_4$	265	91-92	0.8	1.5	0.8	0.8
*1-Fluoro-3-methyl-4,6-dinitrobenzene[e] Pale yellow cryst.	$C_7H_5FN_2O_4$	200	78-79	3.9	7.9	5.5	0.58
1-Fluoro-3-hydroxy-4,6-dinitrobenzene[f] Pale yellow cryst.	$C_6H_3FN_2O_5$	202	80	130	180	275	150
3,5-Dinitrobenzotrifluoride Pale yellow cryst.	$C_7H_3F_3N_2O_4$	236	49-50	200	-	200	80
NITRO HALIDES							
2,4-Difluoronitrobenzene Yellow liqd.	$C_6H_3F_2NO_2$	159	f.p. 9.75 (207°)[d]	<400	>300	180	-
2,5-Difluoronitrobenzene Yellow liqd.	"	"	f.p.-11.7 (206.5°)[d]	-	-	-	>150
NITROANISOLES							
2,4-Difluoroanisole Colorless liqd.	$C_7H_6F_2O$	144	f.p.-15.5 (151)[d]	ca.1750	-	-	-
2,4-Difluoro-6-nitroanisole Yellow cryst.	$C_7H_5F_2NO_3$	189	33-33.5 (66-67°/3 mm)[d]	ca.1000	-	-	-
BENZOIC ACIDS							
*2,4-Difluorobenzoic Acid White cryst.	$C_7H_4F_2O_2$	158	183-184	350	290	500	525
*2,4,5-Trifluorobenzoic Acid White cryst.	$C_7H_3F_3O_2$	176	97-98	480	475	875	700

APPENDIX I (cont'd)

Name and Appearance of Compound	Compound[a] Empirical Formula	Mol. Wt.	M.p. °C	Concentration as ppm required to prevent growth[b] A. niger	A. terreus	M. verrucaria	C. globosum
BENZYL COMPOUNDS							
*2,4,6-Trifluorobenzyl Chloride[c] Colorless liqd.	C_7H_4ClF	181.5	- [d] (157°)	Very mild fungistatic potency			
*2-Hydroxy-3,5-difluoro-benzyl Alcohol White cryst.	$C_7H_6F_2O_2$	160	61-63	>600	-	-	<600
MISCELLANEOUS							
*2,2',4,4'-Tetrafluoroazo-benzene Yellow cryst.	$C_{12}H_6F_4N_2$	254	146-147	No effect at 1000 ppm		-	-
QUINONES and DERIVATIVES							
2,5-Difluoro-1,4-benzoquinone Yellow cryst.	$C_6H_2F_2O_2$	144	172.5-173.5	5000	375	375	62.5
*2-Chloro-5-fluoro-1,4-benzoquinone Yellow cryst.	$C_6H_2ClFO_2$	160.5	126-127	>500	>500	500	>500
*2-Methyl-5-fluoro-1,4-benzoquinone Yellow cryst.	$C_7H_5FO_2$	140	77-78	Very little fungistatic potency			
*2-Chloro-3,6-difluoro-1,4-benzoquinone Yellow cryst.	$C_6HClF_2O_2$	178.5	146-147	-	>>600	-	>500
*2,5-Dichloro-3,6-difluoro-1,4-benzoquinone (?) Yellow cryst.	$C_6Cl_2F_2O_2$	213	205 (decompn.)	1600	800	-	-

APPENDIX I (concluded)

Name and Appearance of Compound	Compound[a] Empirical Formula	Mol. Wt.	M.p. °C	Concentration as ppm[b] required to prevent growth: A. niger	A. terreus	M. varucaria	C. globosum
*2,5-Difluoro-1,4-hydroquinone (White cryst.)	$C_6H_4F_2O_2$	146	129.5-130.5	4000	-	>500	375
*2,5-Difluoro-1,4-hydroquinone diacetate (White cryst.)	$C_{10}H_8F_2O_4$	230	151-152	-	-	-	1500
2,3,5,6-Tetrachloro-1,4-hydroquinone (White cryst.)	$C_6H_2Cl_4O_2$	248	170-171	95	95	35	45
BIPHENYLS							
*2,2'-Dihydroxy-5,5'-difluoro-biphenyl (White cryst.)	$C_{12}H_8F_2O_2$	222	138-139	140	60	110	37
*3,3'-Difluoro-4,4'-dihydroxybiphenyl (White cryst.)	$C_{12}H_8F_2O_2$	222	189	200	120	127	55
*2,2'-Dihydroxy-3,3',5,5'-tetrafluorobiphenyl (White cryst.)	$C_{12}H_6F_4O_2$	258	173	230	120	205	60
*2,2'-Dihydroxy-5,5'-difluoro-biphenyl sulfide (White cryst.)	$C_{12}H_8F_2O_2S$	254	119	95	72	26.5	24

[a] Also included are compounds studied in WADC Technical Report 52-214 (Nov. 1952). [b] Fungicidal data from L. R. Tehon, Air Force Technical Report 6518, Pts. I, II, III, and IV (Mar. 1951-Jan. 1954). [c] Sample borrowed for test purposes, but synthesized on another project. [d] Boiling point °C. [e] Listed also under nitrotoluenes. [f] Listed also under nitrophenols.

APPENDIX II

COMPOUNDS DELIVERED TO MATERIALS LABORATORY

(Twelve compounds - 1900 g.)

*200 g.	1-Fluoro-3-methyl-4,6-dinitrobenzene	(9/30/53)#
200 g.	1-Fluoro-3-chloro-4,6-dinitrobenzene	(9/30/53)#
200 g.	1-Fluoro-3-bromo-4,6-dinitrobenzene	(9/30/53)#
200 g.	1,3-Difluoro-4,6-dinitrobenzene	(1/7/54)#
200 g.	2,4-Dinitrofluorobenzene	(1/7/54)#
100 g.	4-Fluoro-2,6-dinitrophenol	(12/16/53)#
100 g.	2-Nitro-4-fluorophenol	(2/15/54)#
*100 g.	2-Bromo-4-fluorophenol	(3/2/54)
*100 g.	2,2'-Dihydroxy-5,5'-difluorobiphenyl	(3/27/53)
100 g.	" " "	(3/2/54)
*100 g.	3,3'-Difluoro-4,4'-dihydroxybiphenyl	(4/23/53)
100 g.	" " "	(3/2/54)
*100 g.	2,2'-Dihydroxy-3,3',5,5'-tetrafluorobiphenyl	(3/19/54)
*100 g.	2,2'-Dihydroxy-5,5'-difluorobiphenyl Sulfide	(12/11/53)

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*New compound. #Described in Tech. Rept. No. 52-214.

COMPOUND INDEX

*New compounds (10) tested as fungicides in this report